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ATTORNEYS FOR PLAINTIFF
SCHERING CORPORATION

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SCHERING CORPORATION,

Plaintiff,

v.

ZYDUS PHARMACEUTICALS, USA, INC., SANDOZ INC., MYLAN PHARMACEUTICALS INC., ORGENUS PHARMA, INC., ORCHID CHEMICALS & PHARMACEUTICALS, LTD., L. PERRIGO CO., PERRIGO CO., GLENMARK PHARMACEUTICALS INC., USA, GLENMARK PHARMACEUTICALS, LTD., GEOPHARMA, INC., BELCHER PHARMACEUTICALS, INC., LUPIN PHARMACEUTICALS INC., LUPIN LTD., RANBAXY INC., RANBAXY LABORATORIES LTD., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., CARACO PHARMACEUTICAL LABORATORIES, LTD., SUN PHARMACEUTICAL INDUSTRIES LTD., WATSON PHARMACEUTICALS, INC., and WATSON LABORATORIES, INC.,

Defendants.

Civil Action No. 06-4715 (MLC)

COMPLAINT

Plaintiff Schering Corporation ("Schering"), for its Complaint against Defendants Zydus Pharmaceuticals, USA, Inc. ("Zydus"), Sandoz Inc. ("Sandoz"), Mylan Pharmaceuticals Inc. ("Mylan"), Orgenus Pharma, Inc. ("Orgenus"), Orchid Chemicals & Pharmaceuticals Ltd. ("Orchid Ltd."), L. Perrigo Company ("L. Perrigo"), Perrigo Company ("Perrigo Co."), Glenmark Pharmaceuticals Inc., USA ("Glenmark USA"), Glenmark Pharmaceuticals, Ltd. ("Glenmark Ltd."), GeoPharma, Inc. ("GeoPharma"), Belcher Pharmaceuticals, Inc. ("Belcher"), Lupin Pharmaceuticals Inc. ("Lupin Pharmaceuticals"), Lupin Limited ("Lupin Ltd."), Ranbaxy Inc., Ranbaxy Laboratories Limited ("Ranbaxy Laboratories"), Dr. Reddy's Laboratories, Inc. ("DRLI"), Dr. Reddy's Laboratories, Ltd. ("DRLL"), Caraco Pharmaceutical Laboratories, Ltd. ("Caraco"), Sun Pharmaceutical Industries Ltd. ("Sun Ltd."), Watson Pharmaceuticals, Inc. ("Watson Pharmaceuticals"), and Watson Laboratories, Inc. ("Watson Laboratories"), (collectively, "Defendants"), hereby alleges as follows.

Parties

1.A. Plaintiff Schering is a New Jersey corporation having places of business throughout New Jersey, including a place of business at 3070 Route 22 West, Branchburg, New Jersey 08876.

1.B. Upon information and belief, Defendant Zydus is a New Jersey corporation having a place of business at 508 Carnegie Center, Princeton, New Jersey 08540.

1.C. Upon information and belief, Defendant Sandoz is a Delaware corporation having a place of business at 506 Carnegie Center, Princeton, New Jersey 08540.

1.D. Upon information and belief, Defendant Mylan is a West Virginia corporation having a place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26504. Upon information and belief, Defendant Mylan is registered to do business in New

Jersey and has appointed Corporation Service Company of West Trenton, New Jersey as its registered agent in New Jersey for the receipt of service of process.

1.E. Upon information and belief, Defendant Orgenus is a New Jersey corporation and wholly owned subsidiary, agent and alter-ego of Defendant Orchid Ltd. having a place of business at 116 Village Boulevard, Princeton, New Jersey 08540.

1.F. Upon information and belief, Defendant Orchid Ltd. is an Indian corporation having a place of business at Plot No. B3-B6 & B11-B14, Sipcot Industrial Park, Irungattukottai, Sriperumbudur (TK) - 602 105, Kancheepuram District, Tamil Nadu, India. Upon information and belief, Defendant Orchid Ltd. is registered to do business in New Jersey and has appointed Corporation Service Company of West Trenton, New Jersey as its registered agent in New Jersey for the receipt of service of process.

1.G. Upon information and belief, Defendant L. Perrigo is a Michigan corporation and wholly owned subsidiary, agent and alter-ego of Defendant Perrigo Co. having a place of business at 71 Suttons Lane, Piscataway, New Jersey 08854.

1.H. Upon information and belief, Defendant Perrigo Co. is a Michigan corporation having a place of business at 515 Eastern Avenue, Allegan, Michigan 49010. Upon information and belief, Defendant Perrigo Co. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly owned subsidiary, agent and alter-ego Defendant L. Perrigo.

1.I. Upon information and belief, Defendant Glenmark USA is a Delaware corporation and wholly owned subsidiary, agent and alter-ego of Defendant Glenmark Ltd. having a place of business at 750 Corporate Drive, Mahwah, New Jersey 07430.

1.J. Upon information and belief, Defendant Glenmark Ltd. is an Indian corporation having a place of business at Glenmark House, HDO–Corporate Building, Wing -A, B. D. Sawant Marg, Chakala, Off Western Express Highway, Andheri [East], Mumbai 400 099, India. Upon information and belief, Defendant Glenmark Ltd. has appointed Dr. Vijay Soni, Executive Vice President – IP of Defendant Glenmark USA, which is located at 750 Corporate Drive, Mahwah, New Jersey 07430, as its agent in New Jersey for the receipt of any service of process in this action.

1.K. Upon information and belief, Defendant GeoPharma is a Florida corporation having a place of business at 6950 Bryan Dairy Road, Largo, Florida 33777. Upon information and belief, Defendant GeoPharma manufactures numerous products for sale and use throughout the United States, including in this judicial district, including through its subsidiaries, agents and alter-egos.

1.L. Upon information and belief, Defendant Belcher is a Florida corporation and wholly owned subsidiary, agent and alter-ego of Defendant GeoPharma having a place of business at 6950 Bryan Dairy Road, Largo, Florida 33777.

1.M. Upon information and belief, Defendant Lupin Pharmaceuticals is a Virginia corporation and wholly owned subsidiary, agent and alter-ego of Defendant Lupin Ltd. having a place of business at Harborplace Tower, 111 South Calvert Street, Baltimore, Maryland 21202. Upon information and belief, Defendant Lupin Pharmaceuticals is registered to do business in New Jersey and has appointed National Registered Agents, Inc. of Princeton, New Jersey as its registered agent in New Jersey for the receipt of service of process.

1.N. Upon information and belief, Defendant Lupin Ltd. is an Indian corporation having a place of business at 159 CST Road, Kalina, Santacruz (E), Mumbai 400

098, India. Upon information and belief, Defendant Lupin Ltd. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly owned subsidiary, agent and alter-ego Defendant Lupin Pharmaceuticals.

1.O. Upon information and belief, Defendant Ranbaxy Inc. is a Delaware corporation and wholly owned subsidiary, agent and alter-ego of Defendant Ranbaxy Laboratories having a place of business at 600 College Road East, Princeton, New Jersey, 08540.

1.P. Upon information and belief, Defendant Ranbaxy Laboratories is an Indian corporation having a place of business at Plot 90, Sector 32, Gurgaon -122001 (Haryana), India. Upon information and belief, Defendant Ranbaxy Laboratories manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly owned subsidiary, agent and alter-ego Defendant Ranbaxy Inc.

1.Q. Upon information and belief, Defendant DRLI is a New Jersey corporation and wholly owned subsidiary, agent and alter-ego of DRLL having a place of business at 200 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807.

1.R. Upon information and belief, Defendant DRLL is an Indian corporation having a place of business at 7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh, India. Upon information and belief, Defendant DRLL manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly owned subsidiary, agent and alter-ego Defendant DRLI. Upon information and belief, Defendant DRLL has appointed Lee Banks, Esq. of Defendant DRLI, which is located at 200 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807, as its agent in New Jersey for the receipt of any service of process in this action.

1.S. Upon information and belief, Defendant Caraco is a Michigan corporation having a place of business at 1150 Elijah McCoy Drive, Detroit, Michigan 48202. Upon information and belief, Caraco manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

1.T. Upon information and belief, Defendant Sun Ltd. is an Indian corporation having a place of business at Acme Plaza, Andheri - Kurla Rd, Andheri (E), Mumbai - 400 059 and a manufacturing facility in Cranbury, New Jersey. Upon information and belief, Defendant Sun Ltd. itself and through its agent Defendant Caraco manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

1.U. Upon information and belief, Defendant Watson Pharmaceuticals is a Nevada corporation and parent, agent and alter-ego of Defendant Watson Laboratories having a place of business at 360 Mt. Kemble Avenue, Morristown, New Jersey 07962. Upon information and belief, Defendant Watson Pharmaceuticals markets numerous drugs throughout the United States, including in this judicial district.

1.V. Upon information and belief, Defendant Watson Laboratories is a Nevada corporation having a place of business at 311 Bonnie Circle, Corona, California 92880. Upon information and belief, Defendant Watson Laboratories manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

Nature of the Action

2. This is a civil action for the infringement of United States Patent No. 6,100,274 ("the '274 patent") and United States Patent No. 6,979,463 ("the '463 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. §1 *et seq.*

Jurisdiction and Venue

3. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

4. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or participated in the commission of, a tortious act of patent infringement that has led to foreseeable harm and injury to a New Jersey corporation, Plaintiff Schering, in New Jersey. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

5. This Court has personal jurisdiction over Defendant Zydus by virtue of the fact that, *inter alia*, Zydus is a New Jersey corporation.

6. This Court has personal jurisdiction over Defendant Sandoz by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

7. This Court has personal jurisdiction over Defendant Mylan by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

8. This Court has personal jurisdiction over Defendant Orgenus by virtue of the fact that, *inter alia*, Orgenus is a New Jersey corporation.

9. This Court has personal jurisdiction over Defendant Orchid Ltd. by virtue of, *inter alia*: (1) its presence in New Jersey through its subsidiary, agent and alter-ego; and (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

10. This Court has personal jurisdiction over Defendant L. Perrigo by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

11. This Court has personal jurisdiction over Defendant Perrigo Co. by virtue of, *inter alia*: (1) its presence in New Jersey through its subsidiary, agent and alter-ego; and (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

12. This Court has personal jurisdiction over Defendant Glenmark USA by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

13. This Court has personal jurisdiction over Defendant Glenmark Ltd. by virtue of, *inter alia*: (1) its presence in New Jersey through its appointed agent and its subsidiary, agent and alter-ego; (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

14. This Court has personal jurisdiction over Defendant GeoPharma by virtue of, *inter alia*: (1) its specific contacts with New Jersey in connection with this case; and (2) its systematic and continuous contacts with New Jersey, including through its subsidiaries, agents and alter-egos.

15. This Court has personal jurisdiction over Defendant Belcher by virtue of, *inter alia*: (1) its specific contacts with New Jersey in connection with this case; and (2) its systematic and continuous contacts with New Jersey through its parent, agent and alter-ego.

16. This Court has personal jurisdiction over Defendant Lupin Pharmaceuticals by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

17. This Court has personal jurisdiction over Defendant Lupin Ltd. by virtue of, *inter alia*: (1) its presence in New Jersey through its subsidiary, agent and alter-ego; (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

18. This Court has personal jurisdiction over Defendant Ranbaxy Inc. by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

19. This Court has personal jurisdiction over Defendant Ranbaxy Laboratories by virtue of, *inter alia*: (1) its presence in New Jersey through its subsidiary, agent and alter-ego; (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

20. This Court has personal jurisdiction over Defendant DRLI by virtue of the fact that, *inter alia*, DRLI is a New Jersey corporation.

21. This Court has personal jurisdiction over Defendant DRLI by virtue of, *inter alia*: (1) its presence in New Jersey, including through its subsidiary, agent and alter ego; and (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

22. This Court has personal jurisdiction over Defendant Caraco by virtue of, *inter alia*, its systematic and continuous contacts with New Jersey.

23. This Court has personal jurisdiction over Defendant Sun Ltd. by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey, including through its agents and operating entities.

24. This Court has personal jurisdiction over Defendant Watson Pharmaceuticals, Inc. by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

25. This Court has personal jurisdiction over Defendant Watson Laboratories by virtue of, *inter alia*: (1) its presence in New Jersey through its parent, agent and alter-ego; (2) its systematic and continuous contacts with New Jersey, including through its parent, agent and alter-ego.

26. Venue is proper in this judicial district as to each defendant pursuant to 28 U.S.C. §§ 1391(b), (c) and/or (d) and 1400(b).

The Patents

27. On August 8, 2000, the '274 patent, titled "8-Chloro-6,11-Dihydro-11-(4-Piperidylidine)-5H-Benzo[5,6]Cyclohepta[1,2-b]Pyridine Oral Compositions," was duly and legally issued to Schering as assignee. Since that time, Schering has been, and continues to be, the sole owner of the '274 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '274 patent is attached hereto as Exhibit A.

28. On December 27, 2005, the '463 patent, titled "Stable Extended Release Oral Dosage Composition," was duly and legally issued to Schering as assignee. Since that time, Schering has been, and continues to be, the sole owner of the '463 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '463 patent is attached hereto as Exhibit B.

Acts Giving Rise to this Action

Count I – Infringement of the '274 Patent by all Defendants

29. Upon information and belief, on or after June 21, 2006, Defendants submitted Abbreviated New Drug Applications ("ANDAs") 78-351 through 78-362, 78-364, 78-366 and 78-367 to the U.S. Food and Drug Administration ("FDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). These ANDAs seek the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic versions of certain Schering Clarinex® brand desloratadine products. ANDAs 78-351 through 78-362, 78-364, 78-366 and 78-367 specifically seek FDA approval to market the proposed generic versions of Schering's Clarinex® brand products prior to the expiration of the '274 patent.

30. ANDAs 78-351 through 78-362, 78-364, 78-366 and 78-367 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Schering's Clarinex® brand products. Schering received written notification of ANDAs 78-351 through 78-362, 78-364, 78-366 and 78-367 and their § 505(j)(2)(A)(vii)(IV) allegations between August 17, 2006 and August 31, 2006.

31. Defendants' submission of ANDAs 78-351 through 78-362, 78-364, 78-366 and 78-367 to the FDA, including their § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if any of the Defendants commercially uses, offers for sale or sells a proposed generic version of a Schering Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

32. Schering will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count II – Infringement of the '274 Patent by Defendant Zydus

33. Upon information and belief, on or after June 21, 2006, Zydus submitted ANDAs 78-353 and 78-354 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-353 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-353 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent. ANDA 78-354 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic orally disintegrating tablets containing 2.5 and 5 milligrams of desloratadine per tablet. ANDA 78-354 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 2.5 and 5 milligram orally disintegrating tablet products prior to the expiration of the '274 patent.

34. ANDAs 78-353 and 78-354 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Schering's Clarinex® brand products. Schering received written notification of ANDA 78-353 and its § 505(j)(2)(A)(vii)(IV) allegation on August 18, 2006 and of ANDA 78-354 and its § 505(j)(2)(A)(vii)(IV) allegation on August 17, 2006.

35. Zydus's submission of ANDAs 78-353 and 78-354 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '274 patent under 35

U.S.C. § 271(e)(2)(A). Moreover, if Zydus commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

36. Schering will be irreparably harmed by Defendant Zydus's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count III – Infringement of the '274 Patent by Defendant Sandoz

37. Upon information and belief, on or after June 21, 2006, Defendant Sandoz submitted ANDA 78-364 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-364 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-364 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

38. ANDA 78-364 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-364 and its § 505(j)(2)(A)(vii)(IV) allegation on August 30, 2006.

39. Sandoz's submission of ANDA 78-364 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Sandoz commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

40. Schering will be irreparably harmed by Defendant Sandoz's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count IV– Infringement of the '274 Patent by Defendant Mylan

41. Upon information and belief, on or after June 21, 2006, Defendant Mylan submitted ANDA 78-351 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-351 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-351 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

42. ANDA 78-351 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-351 and its § 505(j)(2)(A)(vii)(IV) allegation on August 23, 2006.

43. Mylan's submission of ANDA 78-351 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Mylan commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

44. Schering will be irreparably harmed by Defendant Mylan's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count V – Infringement of the '274 Patent by Defendants Orgenus and Orchid Ltd.

45. Upon information and belief, on or after June 21, 2006, Defendant Orchid Ltd., through its subsidiary, agent and alter-ego Defendant Orgenus, submitted ANDAs 78-356 and 78-357 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-357 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-357 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent. ANDA 78-356 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic orally disintegrating tablets containing 2.5 and 5 milligrams of desloratadine per tablet. ANDA 78-356 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 2.5 and 5 milligram orally disintegrating tablet products prior to the expiration of the '274 patent.

46. ANDAs 78-356 and 78-357 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Schering's Clarinex® brand products. Schering received written notification of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations on August 30, 2006.

47. Orchid Ltd.'s submission of ANDAs 78-356 and 78-357 to the FDA through its subsidiary, agent and alter-ego Orgenus, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Orchid Ltd. and/or Orgenus commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

48. Orgenus is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Orgenus participated in, contributed to, aided, abetted and/or induced the submission of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

49. Orgenus's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Orgenus commercially manufactures, uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

50. Schering will be irreparably harmed by Defendant Orchid Ltd.'s and Defendant Orgenus's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count VI – Infringement of the '274 Patent by Defendants L. Perrigo and Perrigo Co.

51. Upon information and belief, on or after June 21, 2006, Defendant Perrigo Co. submitted ANDA 78-361 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-361 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-361 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

52. ANDA 78-361 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by

the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-361 and its § 505(j)(2)(A)(vii)(IV) allegation on August 29, 2006.

53. Perrigo Co.'s submission of ANDA 78-361 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Perrigo Co. commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

54. Perrigo Co.'s subsidiary, agent and alter-ego Defendant L. Perrigo is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, L. Perrigo participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-361 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Additionally, upon information and belief, L. Perrigo will, without authority, manufacture its proposed generic version of Schering's Clarinex® brand product in the United States and/or sell it to Perrigo Co. within the United States for subsequent commercial sale by Perrigo Co. if ANDA 78-361 is approved by the FDA.

55. L. Perrigo's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-361 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if L. Perrigo commercially manufactures, uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

56. Schering will be irreparably harmed by Defendant Perrigo Co.'s and Defendant L. Perrigo's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count VII – Infringement of the '274 Patent by Defendants Glenmark USA and Glenmark Ltd.

57. Upon information and belief, on or after June 21, 2006, Defendant Glenmark Ltd. submitted ANDA 78-362 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-362 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-362 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

58. ANDA 78-362 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-362 and its § 505(j)(2)(A)(vii)(IV) allegation on August 30, 2006.

59. Glenmark Ltd.'s submission of ANDA 78-362 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Glenmark Ltd. commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

60. Glenmark Ltd.'s subsidiary, agent and alter-ego Defendant Glenmark USA is jointly and severally liable for any infringement of the '274 patent. This is so because, upon

information and belief, Glenmark USA participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-362 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Additionally, upon information and belief, Glenmark USA will, without authority, market and/or distribute its proposed generic version of Schering's Clarinex® brand product in the United States if ANDA 78-362 is approved by the FDA.

61. Glenmark USA's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-362 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Glenmark USA commercially manufactures, uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

62. Schering will be irreparably harmed by Defendant Glenmark Ltd.'s and Defendant Glenmark USA's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count VIII – Infringement of the '274 Patent by Defendants GeoPharma and Belcher

63. Upon information and belief, on or after June 21, 2006, Defendant GeoPharma, through its subsidiary, agent and alter-ego Defendant Belcher, submitted ANDA 78-355 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-355 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-355 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

64. ANDA 78-355 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-355 and its § 505(j)(2)(A)(vii)(IV) allegation on August 22, 2006.

65. GeoPharma's submission of ANDA 78-355 to the FDA, through Belcher, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if GeoPharma commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

66. Belcher is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Belcher participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-355 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA.

67. Belcher's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-355 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Belcher commercially manufactures, uses, offers for sale or sells the proposed generic version of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

68. Schering will be irreparably harmed by Defendant GeoPharma's and Defendant Belcher's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count IX – Infringement of the '274 Patent by Defendants Lupin Pharmaceuticals and Lupin Ltd.

69. Upon information and belief, on or after June 21, 2006, Defendant Lupin Ltd., through its subsidiary, agent and alter-ego Lupin Pharmaceuticals, submitted ANDA 78-352 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-352 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-352 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

70. ANDA 78-352 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-352 and its § 505(j)(2)(A)(vii)(IV) allegations on August 31, 2006.

71. Lupin Ltd.'s submission of ANDA 78-352 to the FDA, through Lupin Pharmaceuticals, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin Ltd. commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

72. Lupin Pharmaceuticals is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Lupin Pharmaceuticals participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-352

and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Additionally, upon information and belief, Lupin Pharmaceuticals will, without authority, market and/or distribute its proposed generic version of Schering's Clarinex® brand product in the United States if ANDA 78-352 is approved by the FDA.

73. Lupin Pharmaceuticals' participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-352 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin Pharmaceuticals commercially manufactures, uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

74. Schering will be irreparably harmed by Defendant Lupin Ltd.'s and Defendant Lupin Pharmaceuticals' infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count X – Infringement of the '274 Patent
By Defendants Ranbaxy Inc. and Ranbaxy Ltd.

75. Upon information and belief, on or after June 21, 2006, Defendant Ranbaxy Ltd., through its subsidiary, agent and alter-ego Ranbaxy Inc., submitted ANDA 78-360 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-360 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-360 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

76. ANDA 78-360 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-360 and its § 505(j)(2)(A)(vii)(IV) allegation on August 18, 2006.

77. Ranbaxy Ltd.'s submission of ANDA 78-360 to the FDA, through Ranbaxy Inc., including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Ranbaxy Ltd. commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

78. Ranbaxy Inc. is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Ranbaxy Inc. participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-360 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA.

79. Ranbaxy Inc.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-360 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Ranbaxy Inc. commercially manufactures, uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

80. Schering will be irreparably harmed by Defendant Ranbaxy Ltd.'s and Defendant Ranbaxy Inc.'s infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count XI – Infringement of the '274 Patent by Defendants DRLI and DRLL

81. Upon information and belief, on or after June 21, 2006, Defendant DRLL, through its subsidiary, agent and alter-ego Defendant DRLI, submitted ANDAs 78-366 and 78-367 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-366 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine / 240 milligrams of pseudoephedrine per tablet. ANDA 78-366 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product prior to the expiration of the '274 patent. ANDA 78-367 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic orally disintegrating tablets containing 2.5 and 5 milligrams of desloratadine per tablet. ANDA 78-367 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 2.5 and 5 milligram orally disintegrating tablet products prior to the expiration of the '274 patent.

82. ANDAs 78-366 and 78-367 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Schering's Clarinex® brand products. Schering received written notification of ANDAs 78-366 and 78-367 and their § 505(j)(2)(A)(vii)(IV) allegations on August 28, 2006.

83. DRLL's submission of ANDAs 78-366 and 78-367 to the FDA, through DRLI, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '274

patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if DRLL commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

84. DRLI is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, DRLI participated in, contributed to, aided, abetted and/or induced the submission of ANDAs 78-366 and 78-367 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

85. DRLI's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDAs 78-366 and 78-367 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if DRLI commercially manufactures, uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

86. Schering will be irreparably harmed by Defendant DRLL's and Defendant DRLI's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count XII – Infringement of the '463 Patent by Defendants DRLI and DRLL

87. Upon information and belief, on or after June 21, 2006, Defendant DRLL, through its subsidiary, agent and alter-ego Defendant DRLI, submitted ANDA 78-366 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-366 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine / 240 milligrams of

pseudoephedrine per tablet. ANDA 78-366 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product prior to the expiration of the '463 patent.

88. ANDA 78-366 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '463 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product. Schering received written notification of ANDA 78-366 and its § 505(j)(2)(A)(vii)(IV) allegations on August 28, 2006.

89. DRLL's submission of ANDA 78-366, through Defendant DRLI, to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '463 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if DRLL commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product, or induces or contributes to such conduct, it would further infringe the '463 patent under 35 U.S.C. § 271(a), (b) and/or (c).

90. DRLI is jointly and severally liable for any infringement of the '463 patent. This is so because, upon information and belief, DRLI participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-366 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA.

91. DRLI's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-366 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '463 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if DRLI commercially manufactures, uses, offers for sale or sells its proposed generic version of

Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product within the United States, or induces or contributes to any such conduct, it would further infringe the '463 patent under 35 U.S.C. § 271(a), (b) and/or (c).

92. Schering will be irreparably harmed by Defendant DRLL's and Defendant DRLI's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count XIII – Infringement of the '274 Patent by Defendants Caraco and Sun Ltd.

93. Upon information and belief, on or after June 21, 2006, Defendant Sun Ltd. submitted ANDA 78-359 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-359 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-359 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

94. ANDA 78-359 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-359 and its § 505(j)(2)(A)(vii)(IV) allegation on August 28, 2006.

95. Sun Ltd.'s submission of ANDA 78-359 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Sun Ltd. commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

96. Defendant Caraco is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Caraco participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-359 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Additionally, upon information and belief, Caraco will, without authority, market and/or distribute its proposed generic version of Schering's Clarinex® brand product in the United States if ANDA 78-359 is approved by the FDA.

97. Schering will be irreparably harmed by Defendant Sun Ltd.'s and Defendant Caraco's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count XIV – Infringement of the '274 Patent by Defendants Watson Pharmaceuticals and Watson Laboratories

98. Upon information and belief, on or after June 21, 2006, Defendant Watson Laboratories submitted ANDA 78-358 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-358 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-358 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

99. ANDA 78-358 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-358 and its § 505(j)(2)(A)(vii)(IV) allegation on August 25, 2006.

100. Watson Laboratories' submission of ANDA 78-358 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Watson Laboratories commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

101. Upon information and belief, Watson Laboratories' parent, agent and alter-ego Defendant Watson Pharmaceuticals participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-358 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Watson Pharmaceuticals' submission of ANDA 78-358 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA infringed the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Watson Pharmaceuticals commercially manufactures, uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

102. Schering will be irreparably harmed by Defendant Watson Laboratories' and Defendant Watson Pharmaceuticals' infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Prayer for Relief

WHEREFORE, Schering prays for judgment as follows:

A. That all Defendants have infringed the '274 patent and Defendants DRLI and DRLL have infringed the '463 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of any of Defendants' ANDAs identified in this Complaint shall not be earlier than the expiration date of the respective '274 patent or '463 patent, including any extensions;

C. That Defendants, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale or selling the proposed generic versions of Schering's Clarinex® brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '274 patent, prior to the expiration of the '274 patent, including any extensions;

D. That Defendants DRLI and DRLL, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale or selling the proposed generic versions of Schering's Clarinex® brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '463 patent, prior to the expiration of the '463 patent, including any extensions;

E. That Schering be awarded monetary relief if any Defendant commercially uses, offers for sale or sells its proposed generic version of a Schering Clarinex®

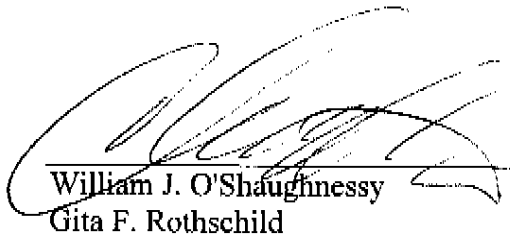
brand product, or any other product that infringes or induces or contributes to the infringement of the '274 or '463 patents, within the United States prior to the expiration of that patent, including any extensions, and that any such monetary relief be awarded to Schering with prejudgment interest;

F. That Schering be awarded the attorney fees, costs and expenses that it incurs prosecuting this action; and

G. That Schering be awarded such other and further relief as this Court deems just and proper.

Dated: September 29, 2006

Respectfully submitted,



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United States Patent [19]

Kou

[11] Patent Number: 6,100,274

[45] Date of Patent: *Aug. 8, 2000

[54] **8-CHLORO-6,11-DIHYDRO-11-(4-PIPERIDYLIDINE)-5H-BENZO[5,6] CYCLOHEPTA[1,2-B]PYRIDINE ORAL COMPOSITIONS**

[75] Inventor: **Jim H. Kou**, Basking Ridge, N.J.

[73] Assignee: **Schering Corporation**, Kenilworth, N.J.

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **09/348,943**

[22] Filed: **Jul. 7, 1999**

Related U.S. Application Data

[60] Provisional application No. 60/092,291, Jul. 10, 1998.

[51] **Int. Cl.**[7] **A61K 31/44**

[52] **U.S. Cl.** **514/290**

[58] **Field of Search** 514/290

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Thomas D. Hoffman

[57] **ABSTRACT**

Stable pharmaceutical compositions containing 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6] cycloheptic[1,2-b]pyridine("DCL") and a DCL protective amount of a pharmaceutically acceptable basic salt such as calcium dibasic phosphate and an amount of at least one disintegrant, preferably two disintegrates such as microcrystalline cellulose and starch sufficient to provide dissolution of at least about 80% by weight of the pharmaceutical composition in about 45 minutes and suitable for oral administration to treat allergic reactions in mammals such as man are disclosed.

40 Claims, No Drawings

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8-CHLORO-6,11-DIHYDRO-11-(4-PIPERIDYLIDINE)-5H-BENZO[5,6] CYCLOHEPTA[1,2-B]PYRIDINE ORAL COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS:

This application claims priority under 35 U.S.C. 119(e) of provisional application Ser. No.: 60/092,291, filed on Jul. 10, 1998.

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions containing 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]-cyclohepta[1,2-b]pyridine (hereinafter "descarbonylethoxyloratadine" or ("DCL") and substantially free of DCL decomposition products, and suitable for oral administration to treat allergic reactions in mammals.

U.S. Pat. No. 4,659,716 discloses descarbonylethoxyloratadine which possesses antihistaminic properties with substantially no sedative properties. This U.S. Patent also discloses methods of making descarbonylethoxyloratadine, pharmaceutical compositions it and methods of using the compositions to treat allergic reactions in mammals.

U.S. Pat. No. 5,595,997 discloses pharmaceutical compositions and methods for treating allergic rhinitis using descarbonylethoxyloratadine. Co-pending, commonly-owned U.S. patent application Ser. No. 08/886,766, filed Jul. 2, 1997 discloses polymorphs of descarbonylethoxyloratadine and pharmaceutical compositions containing them.

We are aware of no prior art that discloses the pharmaceutical compositions of the present invention.

There is a need to produce pharmaceutical compositions suitable for oral administration to mammals and containing descarbonylethoxyloratadine having constant chemical and physical properties in accordance with exacting health registration requirements of the U.S. and international health registration authorities, e.g., the FDA's Good Manufacturing Practices ("GMP") requirements and the International Conference on Harmonization ("ICH") Guidelines.

SUMMARY OF THE INVENTION

We have found that descarbonylethoxyloratadine discolors and decomposes in the presence of excipients disclosed in the prior art. We have discovered that these problems are substantially solved when the use of an acidic excipient is avoided and descarbonylethoxyloratadine is combined with a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of a pharmaceutically acceptable basic salt. Thus, this invention provides a pharmaceutical composition comprising an anti-allergic effective amount of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of a pharmaceutically acceptable basic salt.

The pharmaceutical compositions of the present invention contain less than about 1% of decomposition products such as N-formylDCL initially, as well as when such compositions are stored at 25° C. and about 60% relative humidity for period of at least 24 months.

In a preferred embodiment, this invention provides a pharmaceutical composition comprising an anti-allergic effective amount of descarbonylethoxy-loratadine in a pharmaceutically acceptable carrier medium wherein said composition contains less than about 1% by weight of N-formyl DCL, preferably less than about 0.8% of N-formyl DCL, and more preferably less than about 0.6% of N-formyl DCL.

In another preferred embodiment, this invention provides a pharmaceutical composition for oral administration comprising an anti-allergic effective amount of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of a pharmaceutically acceptable basic salt and an amount of at least one disintegrant sufficient to provide dissolution of at least about 80% by weight of the pharmaceutical composition in about 45 minutes.

This invention also provides a pharmaceutical composition for oral administration comprising an anti-allergic effective amount of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of a calcium dibasic phosphate, and an amount of microcrystalline cellulose and of starch sufficient to provide dissolution of at least about 80% by weight of the pharmaceutical composition in about 45 minutes.

In a preferred embodiment, this invention provides a pharmaceutical composition for oral administration comprising an anti-allergic effective amount of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of a calcium dibasic phosphate, and an amount of microcrystalline cellulose and of starch sufficient to provide dissolution of at least about 80% by weight of the pharmaceutical composition in about 45 minutes, and which contains less than about 1% by weight of N-formyldescarbonyl-ethoxyloratadine.

This invention further provides a preferred pharmaceutical composition for oral administration comprising:

Ingredient	Amount (weight %)
Descarbonylethoxyloratadine	about 0.5–15
Calcium Dibasic Phosphate Dihydrate USP	about 10–90
Microcrystalline Cellulose NF	about 5–60
Corn starch NF	about 1–60
Talc USP	about 0.5–20

This invention also provides another preferred pharmaceutical composition for oral administration comprising:

Ingredient	Amount (weight %)
Descarbonylethoxyloratadine	about 0.5–15
Calcium Dibasic Phosphate Dihydrate USP	about 45–60
Microcrystalline Cellulose NF	about 20–40
Corn starch NF	about 5–15
Talc USP	about 1–10

This invention also provides another preferred pharmaceutical composition for oral administration comprising:

Ingredient	Amount (weight %)
Descarbonylethoxyloratadine	about 1–10
Calcium Dibasic Phosphate Dihydrate USP	about 50–56
Microcrystalline Cellulose NF	about 25–35

-continued

Ingredient	Amount (weight %)
Corn Starch NF	about 10–12
Talc USP	about 2–5

The pharmaceutical compositions of the present invention are useful for treating allergic reactions in mammals.

DETAILED DESCRIPTION OF THE INVENTION

During the development of the compositions of the present invention, descarbonylethoxyloratadine was found to discolor when stored at 75% relative humidity ("RH") and a temperature of 40° C., alone or in combination with various excipients, such as those disclosed in U.S. Pat. Nos. 4,657,716 and 5,595,997. We discovered that this color instability in the active ingredient was apparently due to a very minute amount of a degradation product caused by the presence of a wide variety of excipients commonly used in oral formulations especially a tablet formulation. These excipients found unsuitable include acidic excipients including, but not limited to, stearic acid, povidone, and crospovidone, and other acidic excipients having a pH in water less than 7, preferably in the range of about 3 to 5 as well as other excipients such as lactose, lactose monohydrate, sodium benzoate, and Glyceryl Behenate NF sold under the tradename of Compritol 888 The presence of acidic excipients such as stearic acid in a solid powder formulation blend (similar to that of Example 6) containing DCL, lactose monohydrate, and stearic acid resulted in a large amount (14%) of decomposition of descarbonylethoxyloratadine after one week at 40° C. and 75% RH. When the pharmaceutical compositions of the present invention were subjected to the same stressed conditions for a longer period of time, i.e., 3 months, less than about 1% decomposition of descarbonylethoxyloratadine was found in the pharmaceutical compositions of the present invention. See Examples 1–5, 6 and 10 hereinafter. Preferably, the pharmaceutically acceptable carrier medium used in the pharmaceutical compositions of the present invention should be substantially free, i.e., contain less than about 1% by weight, of acidic excipients.

The major decomposition product of DCL found in the pharmaceutical compositions of the present invention is N-formylDCL. The pharmaceutical compositions of the present invention contain less than about 1% by weight, initially and at periods up to at least 24 months. Preferably, the pharmaceutical compositions of the present invention contain less than about 0.8% by weight, and more preferably they less than about 0.6% by weight of N-formylDCL when such compositions were stored at about 25° C. and about 60% RH for at least 24 months.

The term "pharmaceutically acceptable basic salts" as used herein means a calcium, magnesium or aluminum salt, or mixtures thereof, including, but not limited to carbonates, phosphates, silicates and sulfates of calcium, magnesium and aluminum. Typically suitable pharmaceutically acceptable basic salts include calcium sulfate anhydrous, hydrates of calcium sulfate, such as calcium sulfate dihydrate, magnesium sulfate anhydrous, hydrates of magnesium sulfate, dibasic calcium phosphate, dibasic calcium phosphate anyhdrous, tribasic calcium phosphate, calcium silicate, magnesium silicate, magnesium trisilicate, aluminum silicate, and magnesium aluminum silicate. The use of calcium phosphate salts is preferred. The use of dibasic calcium phosphate hydrates is more preferred The use of dibasic calcium phosphate dihydrate is most preferred.

The DCL-protective amount of the pharmaceutically acceptable basic salt used in the compositions of the present invention is normally about 50% by weight of the total composition. The w/w ratio of the protective amount of the pharmaceutically acceptable basic salt to the anti-allergic amount of DCL is in the range of about 5:1 to about 60:1, preferably about 7:1 to about 11:1, and most preferably about 10:1 to about 11:1.

The term "disintegrant" as used herein means a pharmaceutically acceptable material or combination of such materials that provides a pharmaceutically acceptable dissolution rate for the compositions of the present invention, preferably a dissolution rate for the compositions of the present invention of at least about 80% by weight in about 45 minutes in accordance with the USP paddle dissolution test <711> on page s 1791–1793 of USP 23/NF 18, 1995, UNITED STATES PHARMACOPEIAL CONVENTION, INC., Rockville Md. 20852. Normally, the dissolution rate is measured in 0.1N HCl at 37° C. The preferred dissolution rate of the compositions of the present invention is at least about 80% by weight in about 30 minutes, and more preferably, the dissolution rate of the compositions of the present invention is at least about 90% by weight in about 30 minutes.

Typically suitable pharmaceutically acceptable disintegrants include microcrystalline cellulose, starch, e.g., pregelatinized starch and corn starch, mannitol, croscarmellose sodium and confectioner's sugar (a mixture of at least 95% by weight sucrose and corn starch that has been ground to a fine powder).The pharmaceutical compositions of the present invention contain at least one, preferably at least two, and most preferably two pharmaceutically acceptable disintegrates in the w/w ratio of about 1:1 to 3:1. In a preferred embodiment of the present invention, the two pharmaceutically acceptable disintegrates are cellulose, and starch, preferably corn starch, in the w/w ratio of about 2:1 to about 3:1.

The w/w ratio of the protective amount of the pharmaceutically acceptable basic salt to the amount of the pharmaceutically acceptable disintegrant(s) is in the range of about 1.1:1 to about 2:1, preferably about 1.2:1 to about 1.75:1, and most preferably about 1.20:1 to about 1.25:1.

Unexpectedly, we discovered that when descarbonylethoxyloratadine was combined with a carrier medium comprising dibasic calcium phosphate, and microcrystalline cellulose-in the absence of prior art excipients such as stearic acid, or lactose—we produced a pharmaceutical composition that was stable to discoloration when stored for 4 weeks in open petri dishes at a temperature of 40° C. and relative humidity of 75%. In a preferred embodiment of the present invention, the carrier medium also contains corn starch and talc. In place of the corn starch one may substitute pregelatinized starch; the talc may be replaced by PEG 8000. The calcium dibasic phosphate may be replaced by calcium sulfate dihydrate, but use of calcium dibasic phosphate is preferred. No significant changes (less than about 1–2% by weight) were observed in the physical appearance, moisture content, chemical assay of descarbonylethoxyloratadine and dissolution rate of the tablet formulations when a preferred embodiment of the present invention of Example 10 was stored in plastic bottles or blister packages for up to 9 months at 25° C./60% RH or at 30° C./60% RH or for up to 6 months at 40° C./75% RH.

The descarbonylethoxyloratadine used in the present invention may be prepared in accordance with Example VI of U.S. Pat. No. 4,659,716. Descarbonylethoxyloratadine exists in two polymorphic forms (form 1 and form 2) which may be prepared in accordance with the Examples 1–3 and procedures of commonly-owned co-pending U.S. patent application Ser. No. 08/886,766 filed Jul. 2, 1997. These two polymorphic forms interconverted during the manufacture of the tablets formulation of the present invention. While either polymorph form may be used, form 1 is preferred.

Pharmaceutical Compositions Pharmaceutical compositions of this invention contain an anti-allergically effective amount of descarbonylethoxyloratadine as the active ingredient, and a pharmaceutically acceptable carrier medium which may include, in addition to specific amounts of calcium dibasic phosphate and microcrystalline cellulose, other inert pharmaceutically acceptable ingredients that may be solids or liquids. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets, and suppositories. The inert pharmaceutically acceptable carrier medium includes one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablet disintegration agents or encapsulating materials. The solid dosage forms of the pharmaceutical compositions of the present invention are suitable for oral administration and include powders, tablets, dispersible granules, capsules, cachets, buccals, and suppositories. In powders, the carrier medium is a finely divided solid which is in admixture with the finely divided active ingredient. In the tablet, the active ingredient is mixed with carrier medium having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The anti-allergic effective amount of DCL in the pharmaceutical compositions of this invention, e.g., powders and tablets is from about 0.5 to about 15 percent, preferably about 0.5 to 10 weight percent, and more preferably about 1 to 10 weight percent. The term "compositions" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier medium, which is thus in association with it. Similarly, caches are included.

The anti-allergic effective amount of descarbonylethoxyloratadine for oral administration varies from about 1 to 50 mg/day, preferably about 2.5 to 20 mg/day and more preferably about 5 to 10 mg/day in single or divided doses. The most preferred amount is 5 mg, once a day.

Of course the precise dosage and dosage regimen may be varied depending upon the requirements of the patients (e.g., his or her sex, age) as well as the severity of the allergic condition being treated. Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.

Descarbonylethoxyloratadine possess antihistaminic properties. These antihistaminic properties have been demonstrated in standard animal models, such as prevention of histamine—induced lethality in guinea pigs. Antihistaminic activity of polymorph form 1 and form 2 of descarbonylethoxyloratadine has also been demonstrated in a monkey model.

General Experimental

Descarbonylethoxyloratadine may be prepared in accordance with Example VI of U.S. Pat. No. 4,659,716. Calcium dibasic phosphate dihydrate [$Ca(H_2PO_4)_2.2H_2O$] is available from Rhone Poulenc Rorer, Shelton, Conn. 06484; microcrystalline cellulose is available from FMC Corporation Food & Pharmaceutical Products, Philadelphia, Pa. 19103, corn starch NF is available from National Starch & Chemical Corp., Bridgewater, N.J. 08807 and the talc USP is available from Whittaker, Clark and Daniels, Inc., South Plainfield, N.J.

Method of Manufacture of Pharmaceutical Compositions of the Present Invention in the Form of Tablets

The following procedure illustrates the formulation of tablets:

Starch paste preparation

1. Prepare a 10 w/w starch paste by dispersing the paste portion of corn starch into a portion of purified water in a suitable container equipped with an agitator.
2. While mixing, heat the contents of the container to 95° C. and maintain this temperature for 30 minutes.
3. Add an additional amount of purified water to the heated mixture and allow the so-formed starch paste to cool to approximately 50° C.
4. While mixing, add the descarbonylethoxyloratadine to the starch paste.

Granulation

5. To a suitable fluid bed processing bowl, charge the dibasic calcium phosphate dihydrate, a portion of the corn starch and a portion of the microcrystalline cellulose. Place the processing bowl into a fluid bed processor.
6. Fluidize the powder bed and mix for 3 minutes.
7. Begin granulating the powder by pumping the starch paste of step 4 into the fluidized bed at a suitable spray rate (for a 600,000 tablet batch size, the spray rate was 500 mL/min.) and a bed temperature of 22° C.
8. Continue to dry the granulation at 60° C. until the granulation has a final loss on drying of 2% or less.
9. Pass the dried granulation through a suitable sieve or mill.
10. Charge the granulation to a suitable blender and add the requisite amount of the remaining portion of microcrystalline cellulose, corn starch, and talc. Blend for 5 minutes to produce a uniform powder blend.

The resulting blend may be filled into suitable two-piece hard gelatin capsules on a suitable encapsulating machine. The blend may also be compressed to an appropriate size and weight on a suitable tablet machine.

Tableting

1. Compress the final powder blend on a suitable tablet press with a target tablet weight of 100 mg and hardness of 7–9 s.c.u. (Strong-Cobb Unit(s)

The tablets may be film-coated by charging the compressed tablets into suitable coating equipment having a rotating pan and heater. The tablets on the rotating pan are contacted at a temperature of about 30–50° C. with a coating solutions formed by dissolving clear or colored coating materials in purified water. After the tablets are completely coated, a polishing powder may be added to the coated tablets to provide polished coated tablets. Alternatively, the colored coating material may be added as a dry powder in step 5 or 10, preferably step 5 of the Granulation phase of the process. It is preferred that the colored coating material is preferably substantially free, i.e., < about 1%, or more preferably completely free of offensive excipients such as lactose.

EXAMPLES 1-5

Follow the above-listed manufacturing procedure using the ingredients listed below and compress the powder blend into tablets.

Ingredients	1 mg strength (mg/tab)	2.5 mg strength (mg/tab)	5 mg strength (mg/tab)	7.5 mg strength (mg/tab)	10 mg strength (mg/tab)
Descarbonyl-ethoxylora-tadine	1	2.5	5	7.5	10
Dibasic calcium phosphate dihydrate USP	53	53	53	53	53
Micro-crystalline cellulose NF	32	30.5	28	25.5	23
Corn starch NF	11	11	11	11	11
Talc USP	3	3	3	3	3
Total	100	100	100	100	100

EXAMPLES 6–9

The tablet formulations of Examples 6–9 were prepared in accordance with procedure of Examples 1-5.

Example 6

Ingredients	mg/tablet
Descarbonylethoxyloratadine	10
Lactose monohydrate	69
Corn starch	18
Stearic acid	2
Silicon dioxide	1

Example 7

Ingredients	mg/tablet
Descarbonylethoxyloratadine	10
Lactose monohydrate	59
Microcrystalline cellulose	8
Pregelinized starch	15
Croscarmellose sodium	5
Silicon dioxide	1
Stearic acid	2

Example 8

Ingredients	mg/tablet
Descarbonylethoxyloratadine	2.5
Dibasic calcium phosphate Dihydrate	78.5
Corn starch	18
Magnesium stearate	1

Example 9

Ingredients	mg/tablet
Descarbonylethoxyloratadine	2.5
Microcrystalline cellulose	10
Mannitol	71.5
Pregelinized starch	15
Magnesium stearate	1

The tablet formulations of Examples 6–9 prepared in accordance with procedure of Examples 1–5 discolored rapidly when they were placed in open petri dishes after less than one week under a temperature of 40° C. and a relative humidity of 75%.

Color stability of Formulated Tablets of Examples 1-5

The color stability of the above mentioned tablets of Examples 1–5 was studied in open petri dishes under a stressed condition of a temperature of 40° C. and 75% relative humidity. After storage in the open petri dishes under this condition for 4 weeks, the tablets of Examples 1–5 were found to be free of discoloration and remained white in color. When descarbonyl-ethoxyloratadine was formulated with other excipients such as lactose and stearic acid and formed into tablets, in accordance with the procedures of Examples 1–5, the tablets of Examples 6–9 discolored rapidly after less than one week under the same storage conditions. A solid powder formulation blend(similar to that of the tablets of Examples 6) containing DCL, lactose monohydrate and stearic acid in the w/w/w/ ratio of 1:7:0.2 also decomposed rapidly after less than one week under the same storage conditions of a temperature of 40° C. and 75% relative humidity; the chemical assay for descarbonylethoxyloratadine in this solid powder formulation was about 86% of the initial amount and the color of the formulation was pink.

Example 10

The procedures of Examples 1–5 were followed except that the formulation of Example 3 was compressed into tablets and filmed coated and polished.

Ingredients	mg/tablet
Descarbonylethoxyloratadine	5.0
Dibasic calcium phosphate Dihydrate USP	53.00
Microcrystalline cellulose NF	28.00
Corn starch NF	11.00
Talc NF	3.00
Film coat (blue)	6.00
Film coat (clear)	0.6
Polishing Wax[1]	0.01

[1]The polishing wax is a 1:1 w/w mixture of Carnoba wax and white wax.

The stability of Formulated Tablets of Example 10

Chemical assay, physical properties, and photostability of the formulated tablets of Examples 10 were measured on samples placed in high density polyethylene bottles and blister packages.

No significant changes (<1 2%) were observed in the physical appearance, moisture content, chemical assay of descarbonylethoxyloratadine and dissolution rate when the tablets of Example 10 was stored in plastic bottles or blister packages for up to 9 months at 25° C./60% relative humidity ("RH") or at 30° C./60% RH or for up to 6 months at 40°

C./75% RH. A small amount of degradation, e.g., N-formylDCL, was observed in the tablets stored in bottles (about 0.8%) and in blisters(about 1.2%) at 40 C./75% RH for 6 months; only about 0.2–0.3% of the degradation product was observed in any samples of the tablets stored in blisters or bottles for 9 months at 25° C./60% or at 30° C./60% RH. It is expected that the International Conference on Harmonization("ICH") Impurity Guideline for a 5 mg tablet stored for 24 months at 25° C./60% RH or for 12 months at 30° C./60% RH of 1% by weight of the tablet will be met. When the tablets in an open dish were subjected to ICH light conditions for one week at 25° C., the total amount of decomposition products was 0.31% by weight.

Example 11

The procedures of Examples 10 were followed except that the Blue lake was added as a dry powder to step 5 of the Granulation phase and the formulation was thereafter compressed into tablets

Ingredients	mg/tablet
Descarbonylethoxyloratadine	5.0
Dibasic calcium phosphate Dihydrate USP	53.00
Microcrystalline cellulose NF	27.72
Corn starch NF	11.00
Talc NF	3.00
FD&C Blue #2 Lake	0.28
Total	100.00

The formulation of Example 11 is expected to have similar chemical assay, and physical properties and photostability to that observed for the formulation of Example 10.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled.

What is claimed is:

1. A pharmaceutical composition for oral administration comprising an anti-allergic effective amount of descarbonylethoxy-loratadine in a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of a pharmaceutically acceptable basic salt and at least one pharmaceutically acceptable disintegrant.

2. The pharmaceutical composition of claim 1 wherein the at least one pharmaceutically acceptable disintegrant is in an amount sufficient to provide dissolution of at least 80% by weight of the pharmaceutical composition in about 45 minutes.

3. The pharmaceutical composition of claim 1 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to said disintegrant is in the range of about 1:1 to 2:1.

4. The pharmaceutical composition of claim 1 wherein the pharmaceutically acceptable basic salt is a calcium, magnesium or aluminum salt, or mixtures thereof.

5. The pharmaceutical composition of claim 1 wherein the pharmaceutically acceptable basic salt is a calcium phosphate salt.

6. The pharmaceutical composition of claim 1 wherein the pharmaceutically acceptable carrier medium is substantially free of acidic excipients.

7. A pharmaceutical composition of claim 1 which contains less than about 1% by weight of N-formyldescarbonylethoxyloratadine after storage at about 25° C. and about 60% relative humidity for at least 24 months.

8. The pharmaceutical composition of claim 1 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to the anti-allergic effective amount descarbonylethoxyloratadine is the range of about 5:1 to about 60:1.

9. A pharmaceutical composition for oral administration comprising an anti-allergic effective amount of descarbonylethoxy-loratadine in a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of calcium dibasic phosphate, an amount of microcrystalline cellulose and of starch sufficient to provide dissolution of at least about 80% by weight of the pharmaceutical composition in about 45 minutes.

10. A pharmaceutical composition of claim 9 which contains less than about 1% by weight of N-formyldescarbonylethoxyloratadine after storage at about 25° C. and about 60% relative humidity for at least 24 months.

11. A pharmaceutical composition for oral administration comprising an anti-allergic effective amount of descarbonylethoxy-loratadine in a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of calcium dibasic phosphate, an amount of microcrystalline cellulose and of starch sufficient to provide dissolution of at least 80% by weight of the pharmaceutical composition in about 45 minutes, and containing less than about 1% by weight of N-formyldescarbonyl-ethoxyloratadine after storage at about 25° C. and about 60% relative humidity for at least 24 months.

12. A pharmaceutical composition of claim 9 which comprises:

Ingredient	Amount (weight %)
Descarbonylethoxyloratadine	about 0.5–15
Calcium Dibasic Phosphate Dihydrate USP	about 10–90
Microcrystalline Cellulose NF	about 5–60
Corn starch NF	about 1–60
Talc USP	about 0.5–20.

13. A pharmaceutical composition of claim 9 which comprises:

Ingredient	Amount (weight %)
Descarbonylethoxyloratadine	about 0.5–15
Calcium Dibasic Phosphate Dihydrate USP	about 45–60
Microcrystalline Cellulose NF	about 20–40
Corn starch NF	about 5–15
Talc USP	about 1–10.

14. A pharmaceutical composition of claim 11 wherein the amount of descarbonylethoxyloratadine is in the range of about 1 to about 10 weight percent.

15. A pharmaceutical composition of claim 9 which comprises:

Ingredient	Amount (weight %)
Descarbonylethoxyloratadine	about 1–10
Calcium Dibasic Phosphate Dihydrate USP	about 50–56
Microcrystalline Cellulose NF	about 25–35
Corn Starch NF	about 10–12
Talc USP	about 2–5.

16. The pharmaceutical composition of claim 1 which contains less than about 1% by weight of N-formyldescarbonylethoxyloratadine.

17. A pharmaceutical composition comprising an anti-allergic effective amount of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium comprising a DCL-protective amount of a pharmaceutically acceptable basic salt.

18. The pharmaceutical composition of claim 17 wherein said composition further comprises at least one pharmaceutically acceptable disintegrant.

19. The pharmaceutical composition of claim 18 wherein the at least one pharmaceutically acceptable disintegrant is in an amount sufficient to provide dissolution of at least about 80% by weight of the pharmaceutical composition in about 45 minutes.

20. The pharmaceutical composition of claim 19 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to said disintegrant is in the range of about 1:1 to 2:1.

21. The pharmaceutical composition of claim 18 wherein the pharmaceutically acceptable basic salt is a calcium, magnesium or aluminum salt, or mixtures thereof.

22. The pharmaceutical composition of claim 18 wherein the pharmaceutically acceptable basic salt is a calcium phosphate salt.

23. The pharmaceutical composition of claim 18 wherein the pharmaceutically acceptable carrier medium is substantially free of acidic excipients.

24. A pharmaceutical composition of claim 18 which contains less than about 1% by weight of N-formyldescarbonylethoxyloratadine.

25. The pharmaceutical composition of claim 18 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to the anti-allergic effective amount of descarbonylethoxyloratadine is the range of about 5:1 to about 60:1.

26. A pharmaceutical composition comprising an anti-allergic effective amount of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium wherein said composition contains less than about 1% by weight of N-formylDCL.

27. The pharmaceutical composition of claim 26 wherein said composition is adapted for oral administration.

28. The pharmaceutical composition of claim 26 wherein said composition has been stored at about 25° C. and about 60% relative humidity for at least 24 months.

29. The pharmaceutical composition of claim 1 wherein the w/w ratio of the DCL-protective amount of tje pharmaceutically acceptable basic salt to said disintegrant is in the range of about 1.5:1 to about 2:1.

30. The pharmaceutical composition of claim 1 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to said disintegrant is in the range of about 1.25:1 to about 1.75:1.

31. The pharmaceutical composition of claim 1 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to the anti-allergic effective amount descarbonylethoxyloratadine is the range of 7:1 to about 11:1.

32. The pharmaceutical composition of claim 1 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to the anti-allergic effective amount descarbonylethoxyloratadine is the range of about 10:1 to about 11:1.

33. The pharmaceutical composition of claim 19 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to said disintegrant is in the range of about 1.5:1; to about 2:1.

34. The pharmaceutical composition of claim 19 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to said disintegrant is in the range of about 1.25:1 to about 1.75:1.

35. The pharmaceutical composition of claim 18 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to the anti-allergic effective amount of descarbonylethoxyloratadine is the range of about 7:1 to about 11:1.

36. The pharmaceutical composition of claim 18 wherein the w/w ratio of the DCL-protective amount of the pharmaceutically acceptable basic salt to the anti-allergic effective amount of descarbonylethoxyloratadine is the range of about 10:1 to about 11:1.

37. A pharmaceutical composition comprising an anti-allergic effective amount of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium wherein said composition contains less than about less than about 0.8% of N-formylDCL.

38. A pharmaceutical composition comprising an anti-allergic effective amount of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium wherein said composition contains less than about 0.6% of N-formylDCL.

39. A pharmaceutical composition comprising 5 mg of descarbonylethoxyloratadine in a pharmaceutically acceptable carrier medium.

40. The pharmaceutical composition of claim 39 wherein said composition contains less than about 1% by weight of N-formylDCL.

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(12) **United States Patent**
Kou

(10) **Patent No.: US 6,979,463 B2**
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(54) **STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION**

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(57) **ABSTRACT**

A film-coated extended release solid oral dosage composition containing a nasal decongestant, pseudoephedrine or salt thereof, e.g., pseudoephedrine sulfate in a core effective to provide a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/ml to about 365 ng/ml at a time of about 7.60 hrs to about 8.40 hrs and having two or three film-coatings on the core, the second one containing an amount of the non-sedating antihistamine, desloratadine, effective to provide a geometric maximum plasma concentration of desloratadine of about 2.15 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours, and use of the composition for treating patients showing the signs and symptoms associated with allergic and/or inflammatory conditions of the skin and airway passages are disclosed.

32 Claims, No Drawings

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STABLE EXTENDED RELEASE ORAL DOSAGE COMPOSITION

BACKGROUND OF THE INVENTION

This invention relates to a film-coated extended release solid oral dosage composition containing a nasal decongestant, e.g., pseudoephedrine in a controlled release core and a film outer coating containing the non-sedating antihistamine, desloratadine. The solid oral dosage compositions of this invention are useful for treating patients showing the signs and symptoms associated with allergic and/or inflammatory conditions such as the common cold, as well as signs and symptoms associated with allergic and/or inflammatory conditions of the skin or upper and lower airway passages such as allergic rhinitis, seasonal allergic rhinitis and nasal congestion. upper respiratory diseases, allergic rhinitis and nasal congestion.

Desloratadine, also called descarbethoxyloratadine, is disclosed in U.S. Pat. No. 4,659,716 as a non-sedating antihistamine useful as an anti-allergy agent. U.S. Pat. No. 6,100,274 discloses compositions containing desloratadine. U.S. Pat. No. 5,595,997 discloses methods and compositions for treating seasonal allergic rhinitis symptoms using desloratadine. Desloratadine, upon oral absorption, is hydroxylated at the 3 position to produce the metabolite, 3-hydroxyldesloratadine.

U.S. Pat. Nos. 4,990,535 and 5,100,675 disclose a twice-a-day sustained release coated tablet wherein the tablet coating comprises descarbethoxyloratadine and a hydrophilic polymer and polyethylene glycol, and the tablet core comprises acetaminophen, pseudoephedrine or a salt thereof, a swellable hydrophilic polymer and pharmaceutically acceptable excipients.

U.S. Pat. No. 5,314,697 discloses an extended release tablet containing matrix core comprising pseudoephedrine sulfate and a coating comprising loratadine.

None of the prior art discloses the once-a-day film-coated solid oral dosage composition of this invention.

The successful development of a formulation of a desloratadine-pseudoephedrine once-a-day product would be desirable, but would require achieving a release rate profile for pseudoephedrine component over an extended period in excess of twelve hours and preferably at least 16 hours while maintaining delivery of an effective once a day dose of desloratadine.

It would be desirable for increased patient compliance to have an extended release desloratadine-pseudoephedrine product effective and safe when used on a once-a-day basis for the treatment, management and/or mitigation of the signs and symptoms associated with the common cold, as well as allergic and/or inflammatory conditions of the skin or upper and lower airway passages such as seasonal, allergic rhinitis and nasal congestion.

SUMMARY OF THE INVENTION

We have discovered a desloratadine-pseudoephedrine once-a-day product which produces a release rate profile for pseudoephedrine over an extended period in excess of twelve hours and preferably at least 16 hours while maintaining delivery of an effective once a day dose of desloratadine.

Thus, the present invention provides film-coated extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a film coating uniformly covering the core and comprising an effective amount of desloratadine wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hrs to about 8.40 hrs and the amount of desloratadine is effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

More preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours and a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

Thus, in a preferred embodiment, this invention provides a pharmaceutical composition comprising therapeutically effective amount of pseudoephedrine sulfate in a core and an effective amount of desloratadine in a film coating maintaining the desirable pharmacokinetic parameters of desloratadine, 3-hydroxydesloratadine and pseudoephedrine listed herein above.

This invention also provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising about 240 mg of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a film coating uniformly covering the core and comprising about 5 mg of desloratadine wherein total desloratadine degration products in the film-coated extended release oral dosage composition is less than or equal to about 2.0 weight percent. Preferably, total desloratadine degradation products in the film-coated extended release solid oral dosage composition is less than or equal to 1.0 to about 1.5 weight percent, and more preferably is less than or equal to 0.8 to about 1.0 weight percent, after storage of the compositions at 25 C and 60% relative humidity for at least about 24 months.

The major desloratadine degradation products in the film-coated extended release solid oral dosage composition are (1) N-methyl-desloratadine, and (2) N-formyldesloratadine. See Chart.

This invention also provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising about 240 of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a first film coating uniformly covering the core; and (c) a second film coating uniformly covering the first coating comprising about 5 mg of desloratadine; wherein more than about 90% of the desloratadine in solid oral dosage composition dissolves into a stirred 0.1N HCl solution at 37° C. in about 45 minutes, and more than about 90% of the pseudoephedrine sulfate in solid oral dosage composition dissolves into a stirred 0.1N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. over 16 hours.

This invention also provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or phar-

maceutically acceptable salt thereof, and (b) a film coating uniformly covering the core and comprising an effective amount of desloratadine wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric mean steady state maximum plasma concentration of pseudoephedrine of about 382 ng/mL to about 664 ng/mL at a time of about 5.25 hrs to about 7.99 hrs after administration of a daily dose of said composition for at least about 10 consecutive days, and the amount of desloratadine is effective to produce a geometric mean steady state maximum plasma concentration of desloratadine of about about 1.59 ng/mL to about 3.39 ng/mL at a time of about about 2.24 hours to about 5.12 hours after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state maximum plasma concentration of pseudoephedrine is about 418 ng/mL to about 628 ng/mL at a time of about 5.32 hrs to about 7.98 hrs after administration of a daily dose of said composition for at least about 10 consecutive days, and the geometric mean steady state maximum plasma concentration of desloratadine is about about 1.95 ng/mL to about 2.93 ng/mL at a time of about 2.94 hours to about 4.42 hours after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state maximum plasma concentration of 3-hydroxy-desloratadine of about 1.25 ng/mL to about 1.87 ng/mL at a time of about 3.44 hours to about 5.86 hours and a geometric mean steady state value for the area under the plasma concentration-time curve from 0-24 hours for 3-hydroxy-desloratadine was about 20.3 ng hr/mL to about 3.11 ng hr/mL after administration of a daily dose of said composition for at least about 12 consecutive days

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for desloratadine was about 23.0 ng hr/mL to about 46.6 ng hr/mL.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for desloratadine was about 27.8 ng hr/mL to about 41.8 ng hr/mL.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for pseudo-ephedrine was about 6244 ng hr/mL to about 11346 ng hr/mL.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state value for the area under the plasma concentration-time curve from 0 to 24 hours for pseudoephedrine was about 7030 ng hr/mL to about 10554 ng hr/mL.

The present invention also provides a film-coated extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, and (b) a film coating uniformly covering the core and comprising an effective amount of desloratadine, wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric mean steady state minimum plasma concentration of pseudoephedrine of about 82 ng/mL to about 243 ng/mL after administration of a daily dose of said composition for at least about 10 consecutive days and the amount of desloratadine is effective to produce a geometric mean steady state minimum plasma concentration of desloratadine of about 0.307 ng/mL to about 1.095 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state minimum plasma concentration of pseudoephedrine is about 129 ng/mL to about 193 ng/mL after administration of a daily dose of said composition for at least about 10 consecutive days and the geometric mean steady state minimum plasma concentration of desloratadine is about 0.624 ng/mL to about 0.946 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state minimum plasma concentration of 3-hydroxy-desloratadine of about 0.503 ng/mL to about 0.875 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

Preferred embodiments of the film-coated extended release solid oral dosage composition of the present invention also produce a geometric mean steady state minimum plasma concentration of 3-hydroxy-desloratadine of about 0.551 ng/mL to about 0.827 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days

We have also discovered that by placing a first coating between film-coating comprising desloratadine and the core comprising a nasal decongestant, e.g., pseudoephedrine salt, preferably pseudoephedrine sulfate, provides release of desloratadine from the second film-coating and extended release of the nasal decongestant pseudoephedrine sulfate from the core, preferably a matrix core, over a period in excess of twelve hours while maintaining the desirable pharmacokinetic parameters of desloratadine, 3-hydroxy-desloratadine and pseudoephedrine listed herein above and wherein the total desloratadine degradation products produced is less than or equal 2.0 weight percent, preferably is less than or equal 1.0 to about 1.5 weight percent, and more preferably is less than or equal to 0.8 to about 1.0 weight percent, after storage of the compositions at 25 C and 60% relative humidity for at least about 24 months.

Thus, in a preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a). a matrix core comprising:

1. an extended release amount of a pharmaceutically acceptable decongestant;
2. a polymer matrix;
3. a water insoluble basic calcium, magnesium or aluminum salt;
4. a binder;
5. a lubricant; and optionally,
6. a glidant;

(b) a first film coating uniformly covering the matrix core comprising;

1. a water-swellable film-forming neutral or cationic copolymeric ester;

2. a lubricant;
3. a film-modifier; and
4. optionally, an anti-foaming agent;

(c) a second film coating uniformly covering the first coating, comprising:
1. an immediate release amount of desloratadine;
2. a water-swellable film-forming neutral or cationic copolymeric ester;
3. a lubricant;
4. a water soluble film-modifier; and optionally,
5. an anti-foaming agent;

The film-coated extended release solid oral dosage compositions of the present invention release at least about 80%, and preferably at least about 90% of the desloratadine into a 0.1N HCl solution at 37° C. within about 45 minutes and at least about 50% of the pseudoephedrine sulfate dissolves into a stirred 0.1N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. in 5 hours. and at least about 80% of the pseudoephedrine sulfate dissolves into the stirred solution in 10 hours and at least about 93% of the pseudoephedrine sulfate dissolves into the stirred solution in 16 hours.

In another preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a) a matrix core comprising:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160–480
Ethylcellulose	about 40–120
Dibasic Calcium Phosphate Dihydrate	about 56 -162
Povidone	about 20–60
Silicon Dioxide	about 6–12
Magnesium Stearate	about 2–6
Approximate Matrix Core Weigh Range:	about 518–1082 mg

and

(b) a first film coating uniformly covering the matrix core comprising:
(1) a neutral copolymer of ethyl acrylate and methyl acrylate;
(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;
(3) a polyethylene glycol selected form polyethylene glycol 200 to polyethylene glycol 8000; and
(4) optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel; and

(c) a second film coating uniformly coating the first coating, comprising:
(1) an amount of desloratadine effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;
(2) a neutral copolymer of ethyl acrylate and methyl acrylate;
(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;
(4) a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000; and optionally
(5) a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

The above-listed preferred film-coated extended solid oral dosage composition may further comprise a third film coating uniformly covering the second film coating, wherein the third film coating comprises:
(1) a neutral copolymer of ethyl acrylate and methyl acrylate;
(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;
(3) an effective amount of at least one a water-soluble film-modifying agent selected from low viscosity hydroxypropyl cellulose, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose, and a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000 or mixtures thereof;
(4) a pharmaceutically acceptable dye; and
(5) optionally a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel.

In a more preferred embodiment, the present invention provides a film-coated extended release solid oral dosage composition comprising:

(a) a matrix core comprising:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160–480
Ethylcellulose	about 40–120
Dibasic Calcium Phosphate Dihydrate	about 54–162
Povidone	about 20–60
Silicon Dioxide	about 6–12
Magnesium Stearate	about 2–6
Approximate (Matrix Core) Weight Range:	about 518–1082 mg

(b) a first film coating uniform by covering the matrix core comprising:

	Ingredient	mg/first coating
(d)	a neutral copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800,000;	about 1.36–about 4.08
(2)	a lubricant selected from talc, silicon dioxide and magnesium stearate;	about 1.36–about 4.08
(3)	a polyethylene glycol selected from a polyethylene glycol 6000 to a polyethylene glycol 8000 and	about 0.136–about 0.408
(4)	optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel;	about 0.11–about 0.33
	Total for first film coating: and	about 2.96–8.89 mg

(c) a second film coating uniformly coating the first coating, said second film comprising:

	Ingredient	mg/second film coating
(1)	a 24 hour amount of desloratadine;	about 5.0–about 6.0
(2)	a neutral copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800,000;	about 3.04–about 9.12
(3)	a lubricant selected from talc, silicon dioxide and magnesium stearate;	about 3.5–about 10.5

-continued

(4)	a polyethylene glycol selected from a polyethylene glycol 6000 to a polyethylene glycol 8000; and	about 0.915–about 2.75
(5)	optionally, a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel;	about 0.14–about 042
	Total for second coating:	about 12.60–about 38.79 mg

In a preferred embodiment, the present invention provides a film-coated extended release oral dosage composition comprising:

(a) a matrix core comprising:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 240
Hydroxypropyl Methylcellulose 2208 100,000 cps.	about 160–480
Ethylcellulose	about 40–120
Dibasic Calcium Phosphate	about 56–162
Povidone	about 20–60
Silicon Dioxide; and	about 6–12
Magnesium Stearate	about 2–6
Approximate Matrix Core Weight Range:	about 518–1082 mg

(b) a first film coating uniform by covering the matrix core comprising:

(1) a neutral copolymer of ethyl acrylate and methyl acrylate having molecular weight of 800,000;

(2) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(3) a polyethylene glycol selected from a polyethylene glycol 200 to polyethylene glycol 8000; and

(4) optionally a pharmaceutically acceptable mixture of homologous liquid methyl siloxane polymers and silica gel; and

(c) a second film coating uniformly covering the first coating comprising:

(1) an amount of desloratadine effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/ml. at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;

(2) a netural copolymer of ethyl acrylate and methyl acrylate having an average molecular weight of 800,000;

(3) a lubricant selected from talc, silicon dioxide and magnesium stearate;

(4) a polyethylene glycol selected from a polyethylene glycol 200 to a-polyethylene 8000; and

(5) optionally a pharmaceutically acceptable mixture of homogous liquid methyl siloxane and polymers and silica gel.

A more preferred composition of the present invention is provided herein below:

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg

1. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg

2. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	6.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	5.88
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Subtotal for second coating	20.08 mg

3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating:	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore and Three Coatings) Weight:	842.97 mg

Another more preferred composition of the present invention is provided herein below:

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg

2. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72

-continued

Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating:	5.93 mg

2. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	0.61
Talc NF	5.17
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Hydroxypropyl Methylcellulose 2910 USP 6 cps	3.05
Subtotal for second coating:	20.20 mg

3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.68
Subtotal for third coating	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore & Three Coatings) Weight:	842.37 mg

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudo-ephedrine hydrogen chloride was used in place of pseudoephedrine sulfate.

The compositions of the present invention are useful for treatment of allergic and/or inflammatory conditions of the skin (e.g. urticaria) and the upper and lower airway passages including the nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion in patients in need of such treating.

DETAILED DESCRIPTION OF THE INVENTION

During the course of development of the compositions of the present invention, desloratadine was found to be unstable and to discolor when stored in combination with various excipients such as those disclosed in U.S. Pat. No. 5,314,697 as part of the matrix core containing pseudoephedrine sulfate. The excipients causing discoloration and instability of desloratadine include acidic excipients having a pH of less than 7 in water such as organic acids, such as stearic acid, povidone, crospovidone and carbonyl-containing materials such as lactose, and ethyl cellulose and hydroxylpropyl methylcellulose. Binders like povidone and polymers such as hydroxypropymethylcellulose are useful as a polymer matrix for the sustained release of the pseudoephedrine sulfate from the inner polymer matrix core.

We discovered that by uniformly covering the inner core matrix containing a nasal decongestant, e.g., pseudoephedrine sulfate and hydroxypropyl methylcellulose, ethyl cellulose and povidone with a first coating comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and lubricant, the desloratadine could safely be coated onto the first coating. The desloratadine was found to have an acceptable immediate release profile from the second coating (about 80%, and preferably at least about 90% of the desloratadine is released in 0.1N HCl in less than about 45 min.) and total desloratadine degradation products in the film-coated extended release solid oral dosage composition is less than or equal to 1.0 to about 1.5 weight percent, and more preferably is less than or equal to 0.8 to about 1.0 weight percent, after storage for at least 24 months at 25° C. and about 60% relative humidity ("RH").

When a third film coating comprising a water swellable film-forming neutral or cationic co-polymeric ester and polyethylene glycol as a film modifier was placed on top of the second coating, the dissolution rate of desloratadine from the second coating and pseudoephedrine from the core decreased to unacceptably low levels.

Surprisingly, addition of a low viscosity hydroxylpropyl methylcellulose to the third coating as a film-modifier, restored the dissolution rates of both active ingredients (pseudoephedrine sulfate and desloratadine) to levels approximately the same as those obtained when a core matrix was uniformly covered with two film coatings.

The phrase "allergic and inflammatory conditions of the skin and airway passages" is meant those allergic and inflammatory conditions and symptoms found on the skin and in the upper and lower airway passages from the nose to the lungs. Typical allergic and inflammatory conditions of the skin and upper and lower airway passages include seasonal and perennial allergic rhinitis, non-allergic rhinitis, asthma including allergic and non-allergic asthma, sinusitis, colds (in combination with a NSAID, e.g., aspirin, ibuprofen or acetaminophen) and/or a decongestant e.g. pseudoephedrine), dermatitis, especially allergic and atopic dermatitis, and urticaria and symptomatic dermographism as well as retinophathy, and small vessel diseases, associated with diabetes mellitus.

The amount of desloratadine effective for treating or preventing allergic and inflammatory conditions of the skin and upper and lower airway passages will vary with the age, sex, body weight and severity of the allergic and inflammatory condition of the patient. Typically, the amount of desloratadine effective for treating or preventing such allergic and inflammatory conditions is in the range of about 2.5 mg/day to about 60 mg/day, preferably about 2.5 mg/day to about 20 mg/day, or about 4.0 mg/day to about 15 mg/day, or about 5.0 mg/day to about 10 mg/day, more preferably about 5.0 mg/day to about 10.0 mg/day, and most preferably about 5.0 mg/day to about 6.0 mg/day in a single dose.

Desloratadine is a non-sedating long acting histamine antagonist with potent selective peripheral H1-receptor antagonist activity. Following oral administration, loratadine is rapidly metabolized to descarboethoxyloratadie or desloratadine, a pharmacologically active metabolite. In vitro and in vivo animal pharmacology studies have been conducted to assess various pharmacodynamic effects of desloratadine and loratadine. In assessing antihistamine activity in mice (comparison of ED_{50} value), desloratadine was relatively free of producing alterations in behavior alterations in behavior, neurologic or autonomic function. The potential for desloratadine or loratadine to occupy brain H1-receptors was assessed in guinea pigs following i.p. administration and results suggest poor access to central histamine receptors for desloratadine or loratadine.

In addition to antihistaminic activity, desloratadine has demonstrated anti-allergic and anti-inflammatory activity from numerous in vitro and in vivo tests. These in vitro tests (mainly conducted on cells of human origin) have shown that desloratadine can inhibit many events in the cascade of allergic inflammation. These anti-inflammatory effects for desloratadine are independent of the H1-antagonist effect of

desloratadine and include: The release of inflammatory mediators histamine, truptase, leukotriene and prostaglandin D2 from mast cells;

The release of inflammatory cytokines including IL-4, IL-6, IL-8 and IL-13; The release of the inflammatory chemokines such as RANTES (regulated upon activation, normal T cell expressed and presumably secreted); Superoxide anion production of polymorphonuclear neutrophils; The expression of cell adhesion molecules such as intracellular adhesion molecules (ICAM-1) and P-selection in endothelial cells; and Eosinophil migration and adhesion. In vivo studies also suggest that an inhibitory effect of desloratadine on allergic bronchospasm and cough can also be expected.

The clinical efficacy and safety of desloratadine has been documented in over 3,200 seasonal allergic rhinitis patients in 4 double-blind, randomized clinical trials The results of these chemical studies demonstrated the efficacy of desloratadine in the treatment of adult and adolescent patients with seasonal rhinitis.

The nasal decongestants useful in the present invention include phenylpropanolamine, phenylephrine and and pseudoephedrine. Pseudoephedrine as well as pharmaceutically acceptable acid additional salts, e.g., those of HCl or H_2SO_4, is a sympathominetic drug recognized by those skilled in the art as a safe therapeutic agent effective for treating nasal congestion and is commonly administered orally and concomitantly with an antihistamine for treatment of nasal congestion associated with allergic rhinitis. The use of pseudoephedrine as a nasal decongestant in the present invention is preferred; the use of pseudoephedrine sulfate is more preferred.

In the course of development of the oral dosage composition of this invention, it was discovered that the selection of the polymers for the polymer matrix core was critical to achieve the desired extended release period of at least 12 hours, preferably 12 to 16 hours and more preferably for at least 16 hours for pseudoephedrine sulfate. For example, the use of hydroxypropyl methyl cellulose 4,000 cps or 15,000 cps as polymers in the matrix core did not provide this more preferred extended release period of at least 16 hours for dose of pseudoephedrine sulfate. We discovered that only by selecting for inclusion into the matrix core of specific weight ratios of three specific polymers was the desired pseudoephedrine release profile achieved. Only by combining (1) four parts by weight of hydroxypropyl methyl cellulose 2208 USP, 100,000 cps with (2) one part by weight of ethyl cellulose together with (3) ½ part by weight of povidone as a secondary binder was the more preferred extended release profile of at least 16 hours for pseudoephedrine sulfate from the matrix core achieved. The matrix core also contains specific amounts of silicon dioxide as a glidant and magnesium stearate as a lubricant. The tablet hardness 22±6 Strong-Cobb Units (SCU) is not greatly affected by the higher level of lubricant (6 mg/tablet) but it is preferred to maintain the lubricant level at ⅙ part by weight of lubricant to one part by weight of povidone as secondary binder.

The term "lubricant" as used herein refers to a substance added to the dosage form to enable the dosage form, e.g., a tablet, after it has been compressed to releases from the mold or die.

Suitable lubricants include talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils and the like. Preferably, magnesium stearate or talc is used.

The term "glidants" as used herein refers to a substance, such as an anti-caking agent, which improves the flow characteristics of a powder mixture.

Suitable glidants include silicon dioxide and talc. Preferably, silicon dioxide is used.

The term "binders" as used herein means any material that is added to pharmaceutical compositions to help hold such compositions together and release the medicament therefrom.

Suitable binders are selected from the group consisting of: croscarmellose sodium, a cross-linked polymer of carboxymethylcellulose sodium, povidone, crospovidone, starches, celluloses, alginates, and gums; see also USP XXII page 1858 (1990). Preferably, povidone is used.

Typically suitable antifoaming agents include mixtures of homologous liquid methylsiloxane and silica gel available under the Simethecone tradename.

The term "water-swellable film-forming neutral or cationic copolymeric ester," as used herein means neutral and cationic copolymers of ethyl acrylate and substituted unsubstituted methyl or ethyl methacrylate esters.

Typically suitable water swellable film-forming neutral copolymeric esters include neutral copolymers of ethyl acrylate and methyl metharylate such as are available from Pharma Polymers, a company of the Hüls Group under the EUDRAGIT® Tradename; EUDRAGIT NE30D. and Kollicoat available from BASF, Mt Olive, N.J. An aqueous dispersion containing 30% by weight of a neutral copolymer based on ethyl crylate and methyl methoacrylate (average molecular weight of approximately 800,000) is preferred.

Typically suitable water-swellable film-forming cationic co-polymeric esters include cationic co-polymerers based on dimethylaminoethylmethacrylate and a neutral methacrylic ester such as the EUDRAGIT E copolymers available from Pharma Polymers as a 12.5% solution (EUDRAGIT E 12.5) or as solid (EUDRAGIT E 100) and quaternay ammonium copolymers described in USP/NF as "Amononio methacrylate copolymer, Type A" and Type "B". Such copolymers are available as aqueous dispersions of copolymers of acrylic and methacrylic acid esters with a low (substitution) content of quaternary ammonium groups present as salts, (e.g., quaternary ammonium chlorides). Type A and Type B are available as 30% aqueous dispersions under the EUDRAGIT RL 30D and EUDRAGIT RS 30D tradenames, respectively. Use of the water-swellable film—from neutral co-polymeric esters based on ethyl acrylate and methacrylate is preferred.

The term "water soluble film modifier" as used herein means a film-forming agent which modifies the water-swellable characteristics of the film-forming neutral or cationic copolymeric esters useful in the compositions of the present invention. A typically suitable water soluble film-modifying agent is a low viscosity (≦20 cps) cellulose such as low viscosity hydroxypropyl methyl cellulose, low viscosity hydroxylethyl methyl cellulose; low viscosity sodium carboxymethyl cellulose or a polyethylene glycol selected from polyethylene glycol 200 to polyethylene glycol 8000.

Use of a polyethylene glycol 6000 to polyethylene glycol 8000 as a film modifier is preferred in the first and second coatings; the use of polyethylene glycol 8000 in each coating is more preferred.

Use of polyethylene glycol in combination with a low viscosity hydroxypropyl methylcellulose in the third coating is preferred. Use of a mixture of polyethylene glycol 8000 and hydroxypropyl methylcellulose 2910 cps in the third or outermost film coating is more preferred.

The term "water insoluble basic calcium, magnesium and aluminium salts" as used herein means the pharmaceutically acceptable carbonates, phosphates, silicates and sulfates of calcium, magnesium and aluminum or mixtures thereof.

Typically suitable pharmaceutically acceptable basic salts include calcium sulfate anhydrous, hydrates of calcium sulfate, such as calcium sulfate dihydrate, magnesium sulfate anhydrous, hydrates of magnesium sulfate, dibasic calcium phosphate, dibasic calcium silicate, magnesium trisilicate, magnesium phosphate, aluminum silicate, and hydrates of magnesium phosphate, aluminum phosphate; and calcium phosphate is more preferred. The use of dibasic calcium phosphate dihydrate is most preferred.

The hydroxylpropyl methylcellulose 2910 acts as a film-forming agent in the film coating, and the polyethylene glycols act as film modifier. Other suitable film-forming polymers which may be used include low viscosity (720 cps) hydroxypropyl celluloses, methyl hydroxyethyl cellulose and sodium carboxymethyl cellulose.

The oral dosage composition of this invention also provides a shelf life of more than 24 months, e.g., up to 36 and 48 months so long as the tablets are stored in standard package at between 2° and 30° C. in an ambient environment of 60% relative humidity.

In the preparation of the tablet core, the povidone is dissolved in a mixture of alcohol and water. The pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208 USP, 100,000 cps, ethylcellulose, and dibasic calcium phosphate are blended and granulated with an alcoholic water solution containing povidone. The granulation is milled, and dried to a loss on drying between 0.5 to 2.0%.

The dried granulation is milled and blended with requisite amounts of silicon dioxide and magnesium stearate. The final blend is compressed to produce the inner polymer matrix core composition.

The coatings are normally applied to the inner polymer matrix cores in the following manner:

Cores are charged into a suitable coating pan. A water dispersion of talc, Simethicone, polyethylene glycol 8000 and EUDRAGIT NE30D is applied to the matrix cores as a first coating. These coated matrix cores are then coated with a dispersion of desloratadine, Simethicone, EUDRAGIT NE 30D, polyethylene glycol 8000 NF and talc dispersion. This is followed by an application of third coating containing a dispersion of FD & C Blue No. 2 Aluminum lake containing EDTA as a chelating agent, talc, Simethicone, EUDRAGIT NE30D, containing hydroxy-propyl methylcellulose 2910 cps, and polyethylene glycol 8000 NF. The coated tablets are then branded (with black ink) and packaged in plastic bottles and blisters for storage at a temperature between 2° C. and 30° C. in an ambient environment

During the course of development of the formulations of the present invention, we discovered that the in vitro dissolution studies showed a decrease in both the desloratadine release rate and in desloratadine concentration at increased pH, especially pH values>7.0, compared to those for a 5 mg tablet of desloratadine. The in vivo studies showed the Tmax was greater than 4 hours and that a significant part of the absorptive desloratadine process occurs in the small intestine which has an alkaline pH (pH values>7.0).

We discovered we could increase the release of desloratadine by increasing the level of hydroxypropyl methylcellulose and lowering the levels of the plasticizing agent, e.g., polyethylene glycol 8000, and of the lubricant, e.g., talc, in the second film coating containing desloratadine. See Example 4.

In another preferred embodiment, the effective amount of desloratadine in the second film coating was increased to 6.0 mg and amount of talc was reduced (by about 1.12 mg) to produce an acceptable pharmacokinetic profile. See Example 3 and Table 3.

For the solid oral dosage formulations of the present invention, the geometric mean maximum plasma concentration of pseudoephedrine (PES) is about 345 ng/mL to about 365 ng/mL at a time (Tmax) of about 7.60 hours to about 8.40 hours; the geometric mean maximum plasma concentrate of desloratadine (DL) is about 2.10 ng/mL to about 2.45 ng/mL, preferably 2.15 ng/mL to about 2.35 ng/mL at a time (Tmax), of about 4.0 hours to about 4.5 hours and the geometric mean maximum plasma concentrate of 3-hydroxydesloratadine (3-OH-DL) is about 0.75 ng/mL to about 1.15 ng/mL, preferably about 0.85 ng/mL to about 1.05 ng/mL, and more preferably preferably about 0.88 ng/mL to about 1.02 ng/mL at a time (Tmax) of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition to healthy subjects.

Pharmacokinetic Study No. 1

The pharmacokinetic objective of this study was to determine the bioavailability and bioequivalence of desloratadine (DL), 3-OH DL and pseudoephedrine(PES) from the formulation of Example 2 (5 mg of DL/240 mg of PES) of this application relative to that of a 5 mg of Example 11 of U.S. Pat. No. 6,100,274 (U.S. Pat. No. '274) and an extended-release pseudoephedrine core as references. This study was a Phase I, open-label, single-dose, randomized, three-way crossover study with a seven-day washout period between each treatment. Thirty-six healthy male and female subjects received each of the following treatments in the order assigned by a computer-generated random code:

Treatment A:	One 5 mg DL/240 mg PES tablet of Example 2.
Treatment B:	One DL 5 mg tablet of Example 11 of USP'274.
Treatment C:	One 240 mg pseudoephedrine sulphate (oval extended-release pseudoephedrine cores from Claritin ® D-24 coated with placebo Claritin ® D-24 coat).

The tablets were administered with 180 mL (6 fluid ounces) of non-carbonated room temperature water. The tablet was swallowed whole, not chewed or crushed. After dosing, the oral cavity was inspected to assure that the subject had swallowed the tablet. Subjects continued fasting until the four-hour study procedures were complete. Water was permitted throughout the fasting period, except for two hours post-dose. The subjects remained awake and seated upright/ambulatory for four hours post-dose. All subjects were confined to the study site until the 120-hour blood samples, vital signs and laboratory tests were obtained.

Serial blood samples (10 mL) were to be collected into tubes containing heparin as an anticoagulant at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 48, 72, 96 and 120 hours post-dose. No food was allowed for four hours after dosing. Drinking water was not allowed from one hour pre-dose to one hour postdose, except for the 120 mL administered with the treatment. Plasma concentrations of pseudoephedrine were determined using a validated liquid chromatography with tandem mass spectrometric (LC/MS/MS) method with a lower limit of quantitation (LOQ) of 10.0 ng/mL, and a linear range of 10.0–400 ng/mL. The associated mean pharmacokinetic parameters are provided in Table 1.

The mean DL Cmax following administration of DL tablet of Example 2 of the present invention or a 5 mg desloratadine tablet of Example 11 of U.S. Pat. No. 6,100,274 were 1.79 and 2.23 ng/mL, respectively, and were reached at mean Tmax values of 6.78 and 5.10 hours, respectively.

TABLE 1

Mean (% CV[a]) Pharmacokinetic Parameters of DL, and 3-OH DL in Healthy Subjects Following Single-Dose Oral Administration of DL D-24 and DL

	DL			
	Example 2- 5 mg/240 mg (Treatment A)		Example 11 of USP'274-5 mg (Treatment B)	
Parameter (units)	Mean	% CV	Mean	% CV
Cmax (ng/mL)	1.79	35.8	2.23	34.8
Tmax (hr)	6.78	57.3	5.10	52.5

	3-OH DL			
	Example 2- D-24 5 mg/240 mg (Treatment A)		Example 11 of USP'274 5 mg (Treatment B)	
Parameter (units)	Mean	% CV	Mean	% CV
Cmax (ng/mL)	0.695	59.4	0.832	55.2
Tmax (hr)	6.09[b]	32.7	4.96[b]	31.4

[a]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.
[b]n = 35

The mean 3-OH DL Cmax following administration of 5 mgDL/240 mgPES tablet of Example 2 of this application and a 5 mg desloratadine tablet of Example 11 of U.S. Pat. No. 6,100,274 were 0.695 and 0.832 ng/mL, respectively, and were reached at mean Tmax values of 6.09 and 4.96 hours, respectively. The peak plasma concentration of 3-OH DL decreased slowly with half-life of 29.6 hours following administration of 5 mgDL/240 mgPES tablet of Example 2 of this application, and 29.5 hours following administration of the 5 mg DL tablet of U.S. Pat. No. 6,100,274.

Statistical comparisons of Cmax and AUC(tf) following administration of tablet of Example 2 of this application and 5 mg desloratadine tablet of U.S. Pat. No. 6,100,274 were performed for DK and 3-OH DL plasma concentrations.

The results showed that the 90% confidence intervals for DL and 3-OH DL did not meet the 80–125% bioequivalence guidelines for both Cmax and AUC(tf). For those subjects where AUC(I) could be determined, the confidence intervals of DL for AUC(I) did not meet the 80–125 bioequivancy guidelines. However, the confidence intervals of 3-OH DL for AUC(I) did meet the 80–125 bioequivances guidelines.

The mean pharmacokinetic parameters of pseudoephedrine are provided in Table 2.

TABLE 2

Mean (% CV[a]) Pharmacokinetic Parameters of Pseudoephedrine in Healthy Subjects Following Single-Dose Oral Administration of DL D-24 and 240 mg Pseudoephedrine Sulphate (Oval Extended-Release Pseudoephedrine Cores from Claritin @ D-24 Coated with Placebo Claritin @ D-24 Coat) Tablets (n = 36)

	Pseudoephedrine			
	5 mg/240 mg Tablet of Example 2 of this application		Pseudoephedrine Sulphate (Oval Extended Release Pseudoephedrine Cores from Claritin D-24)	
	Mean	% CV	Mean	% CV
Cmax (ng/mL)	328	25	349	18.1
Tmax (hr)	8.42	34	7.36	36.3
AUC (tf) (ng-hr/mL)	6438	42	6225	38.5
tf (hr)	44.0	37	40.0	25.8
AUC (I) (ng-hr/mL)	6780	40	6452	37.3
t½ (hr)	10.3	148	7.25	21.6

[a]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw Hill, NY, at page 27.

The mean pseudoephedriine Cmax following administration of the (5 mg DL/240 mgPES) tablet of Example 2 or a 240 mg pseudoephedrine sulphate extended-release core were 328 and 349 ng/mL, respectively. Statistical comparisons of Cmax and AUC(tf) values for DL D-24 (5 mg/240 mg) versus 240 mg pseudoephedrine sulphate (extended-release core) were performed. The power to detect a 20% difference in treatment means at an α-level of 0.05 (two-tailed) for the log-transformed Cmax and AUC(tf) were 100 and 93%, respectively.

The 90% confidence intervals for pseudoephedrine met the 80–125% bioequivalence guidelines for both Cmax and AUC(tf). For those subjects were AUC(I) could be determined, the confidence intervals for AUC(I) also met the 80–125 guidelines.

Pharmacokinetic Study No. 2

Subjects were confined at the study site at least 12 hours prior to each treatment (Day −1). In the morning of Day 1, following a ten-hour overnight fast, each subject received one of the following treatments based on his/her subject number and the study period:

Treatment A: One (5 mg DL/240 mgPES) tablet of Example 2 of this application

Treatment B: One (6 mgDL/240 mgPES) tablet of Example 3 of this application

Treatment C: One 5 mg DL tablet of Example 11 of U.S. Pat. No. '274 plus one 120 mg PES tablet (oval extended-release pseudoephedrine core)

The study procedures, blood collection times and the analytical methodologies summarized in Study No. 1 were employed.

The mean pharmacokinetic parameters are shown in Table 3. The power to detect a 20% difference in treatment means of DL at an α-level of 0.05 (two tailed) for the log-transformed AUC(tf), AUC(I), and Cmax values were 89%, 90% and 88% respectively.

TABLE 3

Mean (% CV[1]) Pharmacokinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Adult Volunteers (n = 42) Following Single-Dose Oral Administration of DI Tablets of Examples 2 (5 mg DL/240 mgPES), Example 3 (6 mg DL/240 mg PES) or a 5 mg DL Tablet of USP'274 Plus One 240 mg PES Tablet.

Treatment	Cmax (ng/mL)	% CV	Tmax (hr)/	% CV
	DL			
A[2]	1.91	44	4.69	52
B[3]	2.35	43	4.33	50
C[4]	2.28	40	3.87	67
	3 OH DL			
A[2]	0.77	28	6.67	52
B[3]	1.00	39	6.12	48
C[4]	0.93	31	5.68	58
	Pseudoephedrine			
A[2]	353	30	7.71	45
B[3]	382	28	8.14	46
C[4]	349	22	8.31	47

[1]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.
[2]Treatment A = One (5 mg/240 mg) tablet of Example 2.
[3]Treatment B = One (6 mg/240 mg) tablet of Example 3.
[4]Treatment C = One 5 mg DL tablet of Example II of USP 6,100,274 plus one 240 mg pseudoephedrine tablet.

The results show that, based on plasma 3-OH DL concentrations, the (5 mg/240 mg) of Example 2 is not equivalent to the 5 mg DL tablet of Example 11 of U.S. Pat. No. '274 and that the 6 mgDL/240 PESmg of Example 3 and 5 mg DI. tablet of Example II of U.S. Pat. No. ',274 are bioequivalent.

The results show that, the bioequivalence of pseudoephedrine from the formulations of Examples 2 & 3 was established relative to the reference product.

Pharmacokinetic Study No. 3

Forty health volunteers were enrolled in this open label, randomized, three-way cross-over, single-dose study. The subjects were randomized to receive, following a ten hour over-night fast:

Treatment A:	5 mg DL/240 mg PES of Example 4 of this appln
Treatment B:	DL 5 mg of Example 11 of USP '274 Plus 240 mg PES

The procedures of Study No. 1 were followed using the above-listed treatments.

The mean pharmacokinetic parameters for DL, 3-OH DL and pseudoephedrine are provided in Table 4.

TABLE 4

Mean (% CV[1]) Pharmacokinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Adult Volunteers (n = 40) Following Single-Dose Oral Administration of One 5 mg D-24 Tablet of Example 4 or One 5 mg DL Tablet of USP'274 Plus One 240 mg Pseudoephedrine Sulfate Tablet

Treatment	Cmax (ng/mL)	% CV	Tmax (hr)	% CV
	DL			
A[2]	2.15	41	4.13	66

TABLE 4-continued

Mean (% CV[1]) Pharmacokinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Adult Volunteers (n = 40) Following Single Dose Oral Administration of One 5 mg D-24 Tablet of Example 4 or One 5 mg DL Tablet of USP'274 Plus One 240 mg Pseudoephedrine Sulfate Tablet

Treatment	Cmax (ng/mL)	% CV	Tmax (hr)	% CV
B[3]	2.30	44	4.83	62
	3-OH DL			
A[2]	0.89	48	5.60	42
B[3]	1.07	36	6.10	37
	Pseudoephedrine			
A[2]	382	34	7.83	29
B[3]	399	32	8.43	36

[1]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.
[2]Treatment A = One (5 mgDL/240 mgPES) tablet of Example 4 of application.
[3]Treatment B = One 5 mg DL tablet of Example 11 of USP 6,100,274 plus one 240 mg pseudoephedrine tablet.

Pharmacokinetic Study No. 4

The pharmacokinetic objective of this study was to determine the pharmacokinetic profile of desloratadine (DL), 3-OH DL and pseudoephedrine(PES) following daily administration of the formulation of Example 5 (5 mg of DL/240 mg of PES) of this application for 14 consecutive days This study was a Phase I, open-label, multiple-dose study for 14 consecutive days. Eighteen healthy male and female subjects were enrolled and 17 completed the study; one discontinued. One 5 mg DL/240 mg PES tablet of Example 5. Was administered in the morning (approximately 8 AM)

The tablets were administered with 180 mL (6 fluid ounces) of non-carbonated room temperature water. The tablet was swallowed whole, not chewed or crushed. After dosing, the oral cavity was inspected to assure that the subject had swallowed the tablet. Subjects continued fasting until the four-hour study procedures were complete. Water was permitted throughout the fasting period, except for two hours post-dose. The subjects remained awake and seated upright/ambulatory for four hours post-dose. All subjects were confined to the study site until the 120-hour blood samples, vital signs and laboratory tests were obtained.

Serial blood samples (10 mL) were to be collected into tubes containing heparin as an anticoagulant at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 48, 72, 96 and 120 hours post-dose. No food was allowed for four hours after dosing. Drinking water was not allowed from one hour pre-dose to one hour postdose, except for the 120 mL administered with the treatment. Plasma concentrations of DL, 3-OH DL and pseudoephedrine were determined using a validated liquid chromatography with tandem mass spectrometric (LC/MS/MS) method with a lower limit of quantitation (LOQ) of 0.025 ng/mL, 0.025 ng/mL, and 10.0 ng/mL, respectively. The The methods were validated over concentration range of 0.025 ng/mL—10.0–400 ng/mL for DL, 0.025 ng/mL 10.0–400 ng/mL for 3-OH DL, and 10.0–400 ng/mL for pseudoephedrine. The associated mean steady state pharmacokinetic parameters are provided in Tables 5 & 6.

TABLE 5

Mean (% CV[a]) Steady State Pharmacokinetic Parameters of DL, 3-OH DL and Pseudoephedrine in Healthy Subjects Following Multiple-Dose Oral Administration of DL D-24 For 14 Consecutive Days

	Cmax(ng/mL)		Tmax(hr)		Cavg(ng/mL)		AUC(0–24 h) (ng-hr/mL)	
	Mean	% CV	Mean	% CV	Mean	% CV	Mean	% CV
DL	2.44	35	3.68	39	1.45	34	34.8	34
3-OH DL	1.56	20	4.65	26	1.07	21	25.7	21
Pseudoephedrine	523	27	6.65	31	366	28	8795	29

[a]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw Hill, NY, at page 27.
[b]n = 17

The mean steady state DL Cmax following daily administration of DL tablet of Example 5 of the present invention for 14 consecutive days was 2.44 ng/mL, and was reached at mean Tmax value of 3.68 hours. The mean steady state DL Cavg following administration of tablet was 1.45 ng/mL. The mean steady state AUC(0–24 h) following administration of the tablet was 34.8 ng.hr/mL. The mean 3-OH DL Cmax following administration of 5 mgDL/240 mgPES tablet of Example 5 of this application was 1.56 ng/mL, and was reached at mean Tmax value 4.65 hour. The mean steady state 3-OH DL Cavg was 1.07 ng/mL. The mean steady state AUC((0–24 h) following administration of the tablet was 25.7 ng.hr/mL.

For the solid oral dosage formulations of the present invention, the geometric mean maximum plasma concentration of pseudoephedrine (PES) is about 382 ng/mL to about 664 ng/mL at a time (Tmax) of about 5.25 hours to about 7.99 hours; preferably, about 418 ng/mL to about 628 ng/mL at a time (Tmax) of about 5.32 hours to about 7.98, and a geometric mean steady state value for the area under the plasma concentration-time curve from 0–24 hours for pseudoephedrine was about 6244 ng hr/mL to about 11346 ng hr/mL, preferably, was about 7030 ng hr/mL to about 10554 ng/mL, after administration of a multiple dose of said composition to healthy subjects for at least 10 consecutive days (steady state attained after 10, days data measured over the 14 days), and the geometric mean maximum plasma concentrate of desloratadine (DL) is about 1.59 ng/mL to about 3.39 ng/mL at a time (Tmax) of about 2.24 hours to about 5.12, preferably, 1.95 ng/mL to about 2.93 ng/mL at a time (Tmax), of about 2.94 hours to about 4.42 hours, and a geometric mean steady state value for the area under the plasma concentration-time curve from 0–24 hours for desloratadine was about 23.0 ng hr/mL to about 46.6 ng hr/mL, preferably, was about 27.8 ng hr/mL to about 41.8 ng hr/mL,after administration of a multiple dose of said composition to healthy subjects for at least 12 consecutive days (steady state attained after 12 days data measured over the 14 days), and the geometric mean maximum plasma concentrate of 3-hydroxydesloratadine (3-OH-DL) is about 1.25 ng/mL to about 1.87 ng/mL at a time (Tmax) of about 3.44 hours to about 5.86 hours, and a geometric mean steady state value for the area under the plasma concentration-time curve from 0-24 hours for 3-hydroxy-desloratadine was about 20.3 ng hr/mL to about 3.11 ng hr/mL after administration of a multiple dose of said composition to healthy subjects for at least 12 consecutive days (steady state attained after 12 days, data measured over the 14 days).

The mean trough concentrations of DL, 3-OH DL, and of pseudoephedrine are provided in Table 6.

TABLE 6

Mean (% CV[a]) Pharmacokinetic Parameters of Pseudoephedrine in Healthy Subjects Following Multiple-Dose Oral Administration of DL D-24 (n = 17) For 14 Consecutive Days

	Cmin (ng/ml)		Percent Fluctuation	
	Mean	% CV	Mean	% CV
DL)	0.786	39	115	14
3-OH DL	0.689	27	82.9	18
Pseudoephedrine	161	51	102	22

[a]% CV is percent coefficient of variation, which is a relative measure of variability. See Steele and Torrie, "Principles and Procedures of Statistics", (1980) 2nd Edition, McGraw-Hill, NY, at page 27.

The steady state conditions for DL and 3-OH DL were attained on Day 12 following daily administration of DL as indicated by a lack of a statistically significant difference ($p>0.301$) in the mean trough plasma concentrations of DL between mean trough plasma concentration of DL Day and that on Day 14. The steady state mean trough plasma concentration for pseudoephedrine was attained on Day 10.

For the solid oral dosage formulations of the present invention, the geometric mean minimum plasma concentration of pseudoephedrine (PES) is about 82 ng/mL to about 243 ng/mL, and preferably, about 129 ng/mL to about 193 ng/mL after administration of a multiple dose of said composition to healthy subjects for at least 10 consecutive days (steady state attained after 10 days,data measured over the 14 days), and the geometric mean minimum plasma concentrate of desloratadine (DL) is about 0.307 ng/mL to about 1.095 ng/mL, preferably, 0.624 ng/mL to about 0.946 ng/mL, after administration of a multiple dose of said composition to healthy subjects for at least 12 consecutive days (steady state attained after 12 days, data measured over the 14 days), and the geometric mean minimum plasma concentrate of 3-hydroxydesloratadine (3-OH-DL) is about 0.503 ng/mL to about 0.875 ng/mL, and preferably about 0.551 ng/mL to about 0.827 ng/mL after administration of a multiple dose of said composition to healthy subjects for at least 12 consecutive days (steady state attained after 12 days, data measured over the 14 days).

EXAMPLE 1

This example illustrates preparation of the preferred oral dosage composition of this invention. The ingredients and specific amounts thereof are listed below.

1. Matrix Core

A. Method of Manufacture:

1. Dissolve povidone in a mixture of 3 parts of alcohol and 1 part of purified water.
2. Combine the pseudoephedrine sulfate, hydroxypropyl methylcellulose 2208, ethylcellulose and dibasic calcium phosphate, dihydrate in a suitable mixing bowl and blend under a nitrogen overlay.
3. Granulate the blend from Step 2 with the solution from Step. 1. pass the wet granulation through suitable milling equipment to breakup large lumps.
4. Dry the wet granulation at about 70° C. in a suitable fluid bed processor to a loss on drying between 0.5 to 2.0% as determined by a moisture balance or equivalent.
5. Pass the dried granules through suitable milling equipment.
6. Add the requisite amounts of silicon dioxide and magnesium stearate to the dried, milled granules and blend.
7. Compress the blend on a suitable tablet press.

The matrix cores are coated in the following manners:

A. Preparation of Coating Dispersions and Solutions

1. First Film Coating Solution

(1) Disperse Simethicone and polyethylene glycol 8000 in a portion of purified water and agitate until completely dissolved.

(2) To the product of step 1, add the remainder of the purified water and the talc; stir the so-formed suspension at room temperature until homogeneous.

(3) Slowly add the so-formed homogeneous suspension of step 2 to the stirred EUDRAGIT NE30D dispersion and continue to mix the so-formed mixture until a homogeneous dispersion is formed. Pass the dispersion through a screen.

(4) Spray the dispersion onto the matrix cores maintained at 40° C.±5° C. on a rotating pan.

(5) Dry the coated matrix cores on the rotating pan.

2. Second Film Coating Dispersion

(1) Disperse the Simethicone and polyethylene glycol 8000 in a portion of purified water. Add additional water and stir the dispersion at room temperature until completely dissolved.

(2) Slowly add desloratadine to the dispersion of step 1 and mix until a uniform dispersion is formed. Combine with the talc with the so-formed uniform dispersion, and continue agitation until a homogenous suspension is formed.

(3) Add dispersion of step 2 to the EUDRAGIT NE 30D dispersion and mix until a uniform dispersion is formed. Pass the dispersion through a screen.

(4) Spray the requisite amount of the dispersion from step 3 onto the matrix core with the first coating in a rotating pan at 25–27° C.

(5) Dry the coated matrix cores on the rotating pan.

3. The Third Film Coating Solution

(1) Add the hydroypropyl methylcellulose 2910 to hot purified water (75° C.) and agitate until a solution forms. Cool the so-formed solution to room temperature.

(2) To a separate container, add Simethicone and polyethylene glycol 8000 to purified water and continue to mix until a solution is formed.

(3) Add talc to solution of step 2 and continue to mix until a uniform dispersion is formed.

(4) Add the solution of step 1 to the dispersion of step 3 and continue to mix until

(5) Add FD&C Blue No. 2 aluminum lake containing EDTA as a chelating agent to purified water in a third container and

(6) Add the Blue lake solution of step 5 to the dispersion of step 4 and mix until a homogeneous mixture is formed.

(7) Slowly add the mixture of step 6 to a dispersion of EUDRAG IT NE30D and continue to mix until homogeneous.

(8) Pass dispersion of step 6 through 60 mesh screen.

(9) Spray the requisite amount of the dispersion of step 8 onto the twice-coated matrix cores in a rotating pan at 35°–45° C. Dry the thrice-coated matrix cores in the form of tablets in rotating pan.

(10) Remove the so-formed tablets from pan and further dry at 40° for 16 hours.

EXAMPLE 2

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg
2. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg
3. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	7.00
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Subtotal for second coating	20.20 mg

-continued

4. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating.	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore & Three Coatings) Weight:	842.97 mg

The in vitro dissolution profile of the tablet of Example 1 was measured in a stirred 0.1N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. The 80% of desloratadine in the coating was dissolved within the first 45 minutes and the total dose of pseudoephedrine sulfate in the matrix core was slowly released via erosion and dissolution mechanisms over a period of at least 16 hours.

EXAMPLE 3

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg

2. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg

Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	6.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	5.88
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Subtotal for second coating	20.08 mg

3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	16.24
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore and Three Coatings) Weight:	842.97 mg

EXAMPLE 4

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1.

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg

2. Matrix Core Coatings 1. First Film Coating: Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg

2. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	0.61
Talc NF	5.17
Ethyl Acrylate/Methyl methacrylate neutral copolymer	6.09
Hydroxypropyl Methylcellulose 2910 USP 6 cps	3.05
Subtotal for second coating	20.30 mg

3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Med Blue Dye	3.65
Subtotal for third coating	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore and Three Coatings) Weight:	842.37 mg

EXAMPLE 5

The following more preferred composition of the present invention was made in accordance with the above procedure of Example 1. The formulation of Example 4 was used except in the second film desloratadine layer the amount of polyethylene glycol 8000 was increased to 1.83 mg and the amount of talc was increased to 7.00 and no HPMC 2910 USP 6 cps was added.

1. Matrix Core Ingredient	mg/core
Pseudoephedrine Sulfate USP	240
Hydroxypropyl Methylcellulose 2208 USP 100,000 cps	320
Ethylcellulose NF Type 7	80
Dibasic Calcium Phosphate USP Dihydrate	108
Povidone USP	40
Silicon Dioxide NF	8
Magnesium Stearate NF	4
Approximate Matrix Core Weight:	800 mg
Matrix Core Coatings	
2. Matrix Core Coatings	
1. First Film Coating:	
Ingredient	mg/tablet
Simethicone	0.22
Polyethylene glycol 8000	0.27
Talc NF	2.72
Ethyl Acrylate/Methyl Methacrylate neutral copolymer (30% dispersion in water)	2.72
Subtotal for first coating	5.93 mg
2. Second Film (Immediate Release) Coating	mg/tablet
Desloratadine	5.0
Simethicone	0.28
Polyethylene glycol 8000	1.83
Talc NF	7.00
Ethyl Acrylate/Methyl methacrylate neutral copolymer (30% dispersion in water)	6.09
Subtotal for second coating	20.20 mg
3. Third Film Coating	mg/tablet
Hydroxypropyl Methylcellulose 2910 USP 6 cps	2.09
Talc NF	5.79
Ethyl Acrylate/Methyl Methacrylate Neutral copolymer (30% dispersion in water)	4.18
Polyethylene Glycol 8000 NF	0.42
Simethicone	0.11
Spectra Spray Mud Blue Dye	3.65
Subtotal for third coating	16.24 mg
Approximate Total of Three Coatings Weight:	42.37 mg
Approximate Tablet (MatrixCore and Three Coatings) Weight:	842.37 mg

The total desloratadine degradation products in the film-coated extended release solid oral dosage composition of Example 5 was 0.8 weight percent after storage of the compositions at 25 C and 60% relative humidity for at least about 24 months. The major desloratadine degradation products are (1) N-methyl-desloratadine which was present at a level of about 0.3 weight percent, and (2) N-formyldesloratadine which was present at a level of about 0.4 weight percent.

Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudoephedrine hydrogen chloride was used in place of pseudoephedrine sulfate.

The compositions of the present invention are useful for treatment of allergic and/or inflammatory conditions of the skin (e.g. urticaria) and the upper and lower airway passages including the nasal and non-nasal symptoms of seasonal allergic rhinitis including nasal congestion in patients in need of such treating. The precise dosage and dosage regimen may be varied by the attending clinician in view of the teachings herein depending upon the requirements of the patient, e.g., the patient's age, sex and the severity of the allergic and/or inflammatory condition being treated. Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.

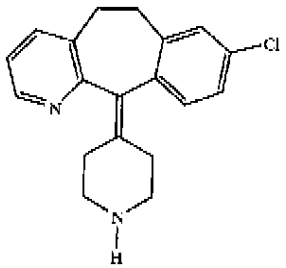
While we have hereinabove presented a number of preferred embodiments of this invention by way of example, it is apparent that the scope of the invention is to be defined by the scope of the appended claims.

The in vitro dissolution profile of the tablets of Examples 1–5 were measured in a stirred 0.1N HCl solution at 37° C. (1st hour) and thereafter in a stirred phosphate buffer having a pH of 7.5 at 37° C. For Example 5, The 91% of desloratadine in the immediate release layer was dissolved within the first 30 minutes, 94% in 45 minutes and 95% of desloratadine was dissolved within 1 hr and the 92–95% of the pseudoephedrine sulfate in the sustained release layer was slowly released via erosion and dissolution mechanisms over a period of at least 16 hours (with 20% in 1 hr, 33% in 2 hrs. and 71% in 8 hrs, 79% in 10 hrs, and 92–95% in 16 hrs).

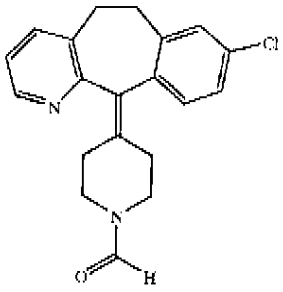
Similar results would be expected if a decongestant effective amount of another pharmaceutically acceptable pseudoephedrine salt, e.g., pseudoephedrine hydrochloride was used in place of pseudoephedrine sulfate.

CHART

I



II



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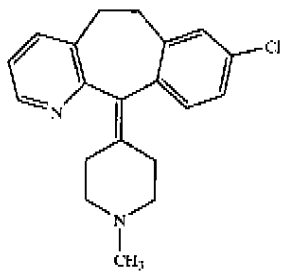

What is claimed is:

1. An extended release solid oral dosage composition comprising (a) a core comprising an effective amount of pseudoephedrine or pharmaceutically acceptable salt thereof, (b) a first coating covering the core and comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and a lubricant, and (c) a second coating covering the first coating and comprising an effective amount of desloratadine, wherein the amount of pseudoephedrine or pharmaceutically acceptable salt thereof is effective to produce a geometric maximum plasma concentration of pseudoephedrine of about 345 ng/mL to about 365 ng/mL at a time of about 7.60 hours to about 8.40 hrs, and the amount of desloratadine is effective to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition.

2. The extended release solid oral dosage composition of claim 1 wherein the amount of desloratadine is effective to produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

3. The extended release solid oral dosage composition of claim 1 wherein the core is a matrix core and wherein the first coating uniformly covers the matrix core and the second coating uniformly covers the first coating.

4. The extended release solid oral dosage composition of claim 3 wherein (a) the first coating comprises

(1) a water-swellable film-forming neutral or cationic co-polymeric ester;

(2) a lubricant;

(3) a film-modifier; and

(4) optionally, an anti-foaming agent;

and wherein (b) the second coating comprises:

(1) an effective amount of desloratadine sufficient to produce a geometric maximum plasma concentration of desloratadine of about 2.10 ng/mL to about 2.45 ng/mL at a time of about 4.0 hours to about 4.5 hours after administration of a single dose of said composition;

(2) a water-swellable film-forming neutral or cationic co-polymeric ester;

(3) a lubricant;

(4) a water soluble film-modifier; and

(5) optionally, an anti-foaming agent

5. The extended release solid oral dosage composition of claim 4 wherein the amount of desloratadine is effective to produce a geometric maximum plasma concentration of 3-hydroxydesloratadine of about 0.75 ng/mL to about 1.15 ng/mL at a time of about 5.50 hours to about 6.25 hours after administration of a single dose of said composition.

6. The extended release solid oral dosage composition of claim 4 which further comprises a third coating covering the second coating, said third coating comprising:

(1) a pharmaceutically acceptable dye;

(2) a water-swellable film-forming neutral or cationic copolymeric ester;

(3) a lubricant;

(4) at least one water soluble film-modifier; and

(5) optionally, an anti-foaming agent.

7. The extended release solid oral dosage composition of claim 6 wherein the water-soluble film-modifier is a low viscosity hydroxypropyl methylcellulose, hydroxyethyl methyl cellulose or sodium carboxymethyl cellulose or a polyethylene glycol selected from polyethylene glycol 200 to a polyethylene glycol 8000, or mixtures thereof.

8. The extended release solid oral dosage composition of claim 4 wherein the matrix core comprises a water-insoluble calcium, magnesium or aluminum salt, wherein the water-insoluble calcium, magnesium or aluminum salt is a carbonate, phosphate, silicate or sulfate of calcium, magnesium or aluminum or mixtures thereof.

9. An extended release solid oral dosage composition comprising (a) a core comprising about 240 mg of pseudoephedrine or pharmaceutically acceptable salt thereof, (b) a first coating covering the core and comprising a water-swellable film-forming neutral or cationic copolymeric ester, a film modifier and a lubricant, and (c) a second coating covering the first coating and comprising about 5 mg of desloratadine wherein total desloratadine degradation products in the extended release oral dosage composition is less than or equal to about 2.0% by weight.

10. The extended release solid oral dosage composition of claim 9 wherein the total desloratadine degradation products comprise less than or about 0.3 to about 0.4% by weight of N-methyldesloratadine, and less than or about 0.4 to about 0.5% by weight of N-formyldesloratadine.

11. The extended release solid oral dosage composition of claim 9 wherein total desloratadine degradation products in the extended release oral dosage composition comprise less than or about 0.8 to about 1.0 weight percent of the composition.

12. The extended release solid oral dosage composition of claim 9 wherein total pseudoephedrine degradation products in the extended release oral dosage composition comprise less than about 0.5 weight percent to no more than about 1.1 weight percent of the composition.

13. The extended release oral dosage composition of claim 1 wherein the matrix core comprises:

Ingredient	mg/core
Pseudoephedrine Sulfate	about 120 to about 360
Hydroxypropyl Methylcellulose 2208, 100,000 cps	about 160 to about 480
Ethylcellulose	about 40 to about 120
Dibasic Calcium Phosphate Dihydrate	about 56 to about 162
Povidone	about 20 to about 60
Silicon Dioxide	about 6 to about 12
Magnesium Stearate	about 2 to about 6.

14. The extended release oral dosage composition of claim 4 wherein the first film coating comprises:

(1) a neutral copolymer of ethyl acrylate and methyl acrylate;

26. The extended release solid oral dosage composition of claim 25 wherein the geometric mean steady state minimum plasma concentration of pseudoephedrine is about 129 ng/mL to about 193 ng/mL after administration of a daily dose of said composition for at least about 10 consecutive days and the geometric mean steady state minimum plasma concentration of desloratadine is about 0.624 ng/mL to about 0.946 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

27. The extended release solid oral dosage composition of claim 25 wherein the amount of desloratadine is effective to produce a geometric mean steady state minimum plasma concentration of 3-hydroxy-desloratadine of about 0.503 ng/mL to about 0.875 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

28. The extended release solid oral dosage composition of claim 25 wherein the amount of desloratadine is effective to produce a geometric mean steady state minimum plasma concentration of 3-hydroxy-desloratadine of about 0.551 ng/mL to about 0.827 ng/mL after administration of a daily dose of said composition for at least about 12 consecutive days.

29. A method of treating allergic and inflammatory conditions of the upper and lower airway passages and skin which comprises administering to a patient in need of such treatment an effective amount of the extended release solid composition of claim 1.

30. A method of treating nasal congestion associated with allergic and inflammatory conditions of the upper and lower airway passages and skin which comprises administering to a patient in need of such treatment an effective amount of the extended release solid composition of claim 1.

31. A method of treating urticaria which comprises administering to a patient in need of such treatment an effective amount of the extended release solid composition of claim 1.

32. A method of treating the nasal and non-nasal symptoms of perennial and seasonal allergic rhinitis which comprises administering to a patient in need of such treatment an effective amount of the extended release solid composition of claim 1.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,979,463 B2
DATED : December 27, 2005
INVENTOR(S) : Kou, Jim H.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 30,
Line 48, replace "psudoephedrine" with -- pseudoephedrine --;
Line 56, replace "the the" with -- the --.

Signed and Sealed this

Eleventh Day of April, 2006

JON W. DUDAS
Director of the United States Patent and Trademark Office